ADVERSE SYMPTOMS OF IMMUNOSUPPRESSANTS: THE PATIENT PERSPECTIVE

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ABSTRACT

Background: Solid organ transplant recipients require lifelong immunosuppressive therapy in order to prevent graft rejection. Unfortunately, these multiple-drug regimens are associated with frequent adverse effects that can negatively impact quality of life (QoL), cause interruptions in treatment, and may even contribute to treatment failure (i.e., graft rejection).

Objectives: To develop and pilot test a survey that characterizes patient perceptions of adverse symptoms of immunosuppressants (ASI), QoL, and medication adherence in a population of patients who have received a solid organ transplant.

Methods: A literature review was undertaken to identify tools assessing patient symptom experience, QoL, and adherence in transplant recipients. A single questionnaire was developed to assess all of these domains. On completion of the survey development phase, the tool was piloted electronically to all adult transplant recipient members of the Canadian Transplant Association. Questionnaires were interpreted using descriptive analysis and frequencies, and respondent's comments were qualitatively assessed using thematic analysis. Feasibility was assessed by response rate, patient's feedback and missing data.

Results: The literature search identified three tools that were incorporated into the questionnaire: the Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD), the Short Form- 12 (SF- 12), and the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS) to measure symptom experience, QoL, and nonadherence to immunosuppressive medications, respectively. The questionnaire was distributed to 249 solid organ transplant recipients and achieved a 51% response rate (n=127). Mean age of survey respondents was 55.5 ±13.2 years, most had good allograft function, few co-morbidities, and reported a similar QoL to that of the general public. More than half of the respondents (61%) received their transplant over 6 years ago, and respondents reported a median of 19 different adverse symptoms (IQR 12- 27). The most prevalent symptoms for both men and women were tiredness, flatulence, and lack of energy (reported at an incidence of 84%, 82% and 70% for women and 80%, 76%, and 66% for men, respectively), while the most distressing symptoms were tiredness, flatulence, and sleeplessness (mean 2.2, 2.2 and 2.1 on a scale of 0 to 4, respectively) in men and joint pain, diarrhea, and lack of energy in women (mean 2.4, 2.4, and 2.3 on a scale of 0 to 4, respectively). Nonadherence to immunosuppressive medications was reported by 29-50% of respondents.

Conclusion: It is feasible to assess symptom experience, QoL and nonadherence to immunosuppressive medications using a single tool in transplant recipients. Despite the high prevalence of adverse symptoms, QoL remained high in members of the Canadian Transplant Association. Wider application of this tool will determine if the findings from this study sample are representative of a general population of patients with solid organ transplants.

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DEDICATION

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CHAPTER 1: INTRODUCTION

Solid organ transplantation is the transfer of human organs from a donor to a recipient with the aim of restoring function in the body. This revolutionary procedure has become the treatment option of choice for patients with kidney failure, and a lifesaving procedure for patients with other types of end-stage organ failure, such as heart, lung or liver failure.

One of the key issues in the field of transplantation is the prevention and management of organ rejection, which occurs when the recipient's immune system recognizes the transplanted organ as foreign. To prevent rejection, transplant recipients must take a complex regimen of immunosuppressive medications.[1] Unfortunately, these medications can cause adverse effects (such as hypertension, infection, diabetes and osteoporosis) as well as adverse symptoms (such as weight gain, increased hair growth and lack of energy).[2-7] Adverse symptoms have not garnered as much attention in transplant literature, likely because they may not be perceived to be as serious, or to be a direct cause of morbidity or mortality. Nevertheless, adverse symptoms can cause significant patient distress, which may impact both quality of life and medication adherence. Further studies are warranted to explore the patient perspective on these adverse symptoms, and to determine the inter-relation between the three areas of symptom experience, quality of life, and nonadherence.

CHAPTER 2: LITERATURE REVIEW

2.1 Background

Organ failure and the need for transplantation are becoming increasingly common in Canada. According to the Canadian Organ Replacement Registry report of 2014, approximately 2456 solid organ transplants were conducted in that year. Of these, there were 1430 kidney, 537 liver, 226 lung, 161 heart and 79 pancreas transplants.[8] Unfortunately, around 4500 patients are still waiting for appropriate donors and 278 people died on the transplant waitlist.[8] These statistics are particularly alarming, since transplantation may be the only option for survival in some individuals with organ failure.[9]

Solid organ transplantation was first performed in the 1960's.[10] Although surgery provided an option for organ failure, the length of patient survival ranged between a few minutes to several months. Unfortunately, the transplanted organ was often rejected by the body, leading to a loss of function and high risk of death.

The human immune system is extremely complex and several pathological mechanisms can contribute to organ transplant rejection. Rejection may be classified according to the timing at which it occurs in relation to the transplant surgery. If rejection occurs within minutes after the transplant it is described as hyperacute rejection. Rejection occurring within days to three months of the transplant is considered acute rejection, and rejection occurring months to years post-transplant is considered chronic rejection. Rejection may be also classified according to histology analyses (cellular-interstitial, vascular, and antibody-endothelial); the severity and the extent of histologic inflammation and injury. It was not until the advent of the immunosuppressive medication cyclosporine in the late 1970's, however, that the problem of organ rejection became more manageable.[11]

It is now realized that a combination of immunosuppressive medications is required to achieve acceptable outcomes in solid organ transplantation. A study of the United Network for Organ Sharing (UNOS) registry in the United States analyzed renal transplant data between the years of 1988 to 1996. The use of maintenance immunosuppressive therapy, consisting of a combination of corticosteroids along with a calcineurin inhibitor (either cyclosporine or tacrolimus), and an antiproliferative agent, resulted in a one-year graft survival rate of approximately 80% -90%.[12]

Immunosuppressive protocols may vary, but in general, they are comprised of the following phases.

1) Induction phase: Peri-operatively, a short course of a potent immunosuppressive is given parentally to the patient to reduce the risks of acute early rejection and allow for the minimization of agents used in the maintenance phase. Examples of immunosuppressive agents used in this phase include polyclonal antibodies such as antithymocyte globulin; or monoclonal antibodies such as basiliximab, or alemtuzumab; and corticosteroids.[13]
2) Maintenance phase: Transplant recipients are required to take a combination of immunosuppressive medications for the life of the graft. These medications, which are used to minimize the incidence of acute and chronic organ transplant rejection, include the calcineurin inhibitors (cyclosporine, tacrolimus), m-tor inhibitors (sirolimus, everolimus), antimetabolites (mycophenolic acid derivatives, azathioprine), and corticosteroids. [13]

In the event of a rejection episode, additional medications are required to minimize graft injury. Agents used may include corticosteroids; polyclonal antibodies such as antithymocyte globulin; and monoclonal antibodies such as alemtuzumab or rituximab; and therapies such as intravenous immune globulin and plasmapheresis.

Immunosuppressive regimens are complex and require constant monitoring to maintain the balance between rejection and drug toxicity. While insufficient immunosuppression in a transplant recipient can lead to organ rejection, over-immunosuppression may increase the risk of infection and risk of malignancy. In addition, these medications can cause a variety of side effects and adverse symptoms for the patient.

There are two major areas of focus in dealing with drug-related side effects. The first issue relates to emerging common post-transplant co-morbid conditions, which can be caused or exacerbated by immunosuppressive medications. Some examples include hypertension, hyperlipidemia, osteoporosis, diabetes, and infections.[2-4,7] Secondly, there are numerous adverse symptoms experienced by transplant recipients. Examples include trembling hands, diarrhea, concentration difficulties, fatigue, headache, muscle weakness, insomnia, and changes in physical appearance. While they may not pose a direct risk to physical health, these adverse symptom experiences can cause significant distress to the transplant recipient. In addition, they may directly or indirectly impact other important outcomes that affect the patient's overall well-

being, quality of life, and activities of daily living. These factors may ultimately influence the patient's motivation to consistently take the medications as prescribed.[14-16] While much attention has been given to the toxicities and co-morbid illnesses associated with immunosuppressive medications, less is known about the overall experiences of transplant patients regarding the adverse symptoms of immunosuppression.

In recent years, however, research has expanded beyond graft rejection and toxicities to consider the patient experience and patient-reported outcomes. Important measures of the post-transplant experience include quality of life (QoL), and symptom experience (adverse symptom occurrence and severity), which may in turn impact medication adherence.[16,17] To understand the interrelation of these three concepts we need to understand their definition.

Quality of life is defined by the World Health Organization as "*the personal perception of an individual of his situation in life, within the cultural context and values in which he lives, and in relation to his objectives, expectations, values and interests*".[18] In related literature, measurement of QoL has been expanded into two aspects. The objective element is based on clinical observations, tests and information whereas the subjective element consists of the patient's perception of well-being, according to his/her own standards. The patient's subjective feelings have been shown to be a crucial factor in adherence to prescribed treatment,[19-21] and may highlight the importance of symptoms that clinicians may overlook or underestimate the frequency and influence of on the patient's daily activities.[6] Other aspects related to quality of life include symptom occurrence and distress. Symptom occurrence describes the prevalence, intensity, and the duration for which a symptom continues to exist, while distress refers to the difficulty that it imparts on the patient to carry on with their daily routine.[22]

Nonadherence has been defined as a "*deviation from the prescribed medication regimen sufficient to adversely influence the regimen's intended effect"*, however other groups have used different definitions.[23] A systematic review of European and North American studies examined nonadherence to immunosuppressive medications among solid organ transplant recipients between 1981 and 2005. This study concluded that nonadherence rates vary between 7/100 cases/year for liver transplant recipients, to as high as 36/100 cases/year for kidney transplant recipients.[24] The measures for nonadherence varied across studies. Some researchers measured adherence according to a specific level of immunosuppressive medications present in blood samples, while others relied on refill rates, or the percentage of medication removed from an

electronic pill bottle. Other researchers yet relied on patient self-reporting. Despite differences in definitions and metrics, it is clear that non-adherence represents a major problem in solid organ transplantation and is a leading cause of poor post-transplant outcomes. Of further importance, rejections caused by nonadherence can negatively impact graft survival and mortality. The previously described systematic review of nonadherence studies showed that a median of 36% graft losses and a median of 14% graft failures were associated with nonadherence.[24]

In a study of 101 heart transplant recipients, nonadherent participants (n=17) experienced 10% more late acute rejections and 12% more re-transplantations compared to adherent participants (n=84) [25]. Adherence was measured for cyclosporine using electronic pill bottles (Medication Event Monitoring System or MEMS). Patients were considered nonadherent if they missed taking their medication within a three hour frame in the morning and evening.[25]

Quality of life, symptom experience and medication adherence seem to be closely related. Examining the relationship between adherence and quality of life was the objective of two studies. The first involved 230 Persian renal transplant recipients, in which a significant correlation was reported between adherence and quality of life scores.[26] Another study of 25 adolescent liver transplant recipients reported a significantly lower QoL for the nonadherent cohort (p=0.001).[27]

Prevalence and intensity of adverse symptoms may collectively contribute to the deterioration in QoL. Consistent struggles with day-to-day activities may affect patient commitment to abide to the prescribed medication regimen, especially for medications perceived to be the cause of these adverse symptoms.[28,29]

To date, most studies have gathered information on one or two domains of symptom experience, patient QoL and adherence. Moreover, several studies have examined symptom experience in populations with only one type of organ transplant. For instance, one study investigated symptom experience in a cohort of patients with heart transplants (n=261).[30] Tiredness, lack of energy, and nervousness were found to be the most common symptoms, noted in 89%, 80% and 75% of patients, respectively. The most distressful symptoms, however, were found to be erectile dysfunction in men (23%), a decreased interest in sex (both genders-16%), and muscle weakness in men (16%).[30]

In a cohort of lung transplant recipients (n=85), researchers compared pre- and post-transplant symptom experience to determine the most frequent and distressing adverse

symptoms. Prior to transplantation the main adverse symptom experienced was dyspnea, while post-transplant the most frequent symptoms included gastrointestinal problems and neurological symptoms, such as tremors.[31]

A study of patients with kidney transplants compared symptom experience between genders.[14] In this study symptoms were classified into low occurrence/low distress, high occurrence/low distress, low occurrence/high distress, and high occurrence/high distress. The most highly occurring and distressful symptoms reported by men (n=207) were tiredness, joint pain, and sleeping disturbances. The least frequent, but very distressing symptoms were anxiety, mouth infections, and swollen gums. The three most highly occurring and distressful adverse symptoms reported by women (n=149) were tiredness, joint pain and brittle skin. The most distressing but infrequently occurring symptoms were painful/excessive menstruation, rash and mouth infections. The investigators in this study concluded that the most frequently occurring symptoms are not necessarily the most distressing.[14]

In a study of 123 liver transplant recipients, investigators characterized symptom experience using the Modified Transplant Symptom Occurrence and Distress scale (29-item version). Liver transplant recipients reported a mean of 16 out of 29 different adverse symptoms (55%). Distress due to symptoms was experienced 1669 times out of 1987 reported symptoms (84%) and it was significantly higher in women compared to males.[16]

One understudied area in transplant literature relates to transplant recipient's perceptions on causality and management of the adverse symptoms they experience. Whether or not a patient perceives something to be treatable may influence how the patient perceives QoL. The perceived cause of the ASI is important as it may influence adherence to medications. Understanding patient attitudes on perceived causes of frequent/troubling symptoms and whether or not they are treatable may provide great insight for health care providers, and assist with the development of patient centered management plans.

Other research examining solid organ transplant recipients collectively have explored adherence. One study consisting of 565 participants (including kidney 48%, liver 47%, and other transplants 5%), examined the effect of urban versus rural residence on self-reported medication adherence. This study showed that 58% of the population was adherent (as measured by the Immunosuppressant Therapy Adherence Scale (ITAS)), and that there was a significant association between living in rural areas and nonadherence.[32]

Most published studies evaluating QoL in solid organ transplantation have been conducted in a single organ cohort (heart, kidney, lung, or liver). In a study of 569 heart transplant recipients, QoL was measured using the Life Satisfaction Index (LSI) and the Transplant Care Index (TCI). Increased QoL scores were significantly associated with age, having a spousal relationship, and having access to a heart specialist as a primary care provider.[33] Somewhat surprisingly, in a cohort of lung transplant recipients (n=17) QoL was relatively comparable to the general population.[34] However, in a study of adolescent liver transplant recipients (n=55), QoL was decreased compared to the general population.[35] A systematic review on this topic described some of these measures that have been used in kidney transplant recipients, including the Short Form-36 (SF-36), Kidney Transplant Questionnaire (KTQ), and the Kidney Disease Quality of Life Instrument (KDQoL).[36] Another recent systematic review identified six generic QoL measures, two disease specific measures, and 12 symptom specific tools. [37]

One study simultaneously examined symptom experience, QoL and adherence in an adolescent renal transplant population. The most frequent symptoms included fatigue, headache, and pimples, while and the most distressing symptoms included moon face, anxiety, and joint pain.[15] QoL was found to be comparable to the non-transplant population, but nonadherence was found in 78% of the cohort. This study, which consisted of only 23 patients, was not designed to study the interrelation between symptom experience, QoL and adherence. To our knowledge no study has contrasted measures of all three domains in any solid organ transplant population.

Patient-reported outcomes are becoming increasingly recognized as important indicators of the impact of disease or treatment strategy on the patient. Patient perceptions and patient-reported outcomes provide a clear picture about the patient's conditions without any external interpretation. Understanding transplant recipient perceptions on their symptom experience, QoL and adherence to immunosuppressive medications may provide health care providers with tools to help facilitate transplant recipients cope with challenges of daily living, and to engage transplant recipients in positive behaviors and self-efficacy. This type of research has become more widely recognized as important, as health-care systems strive to become more patient-centered.

While the value of assessing patient perceptions should be recognized on its own merit, this project is part of a much larger initiative. Optimal management of adverse symptoms from

immunosuppressive medications has not been clearly defined. To address this, a working group consisting of pharmacists and physicians members of the Canadian Society of Transplant (CST) has been established to develop leading practice recommendations on the most effective management of these adverse symptoms. The results of this project will serve to inform as the foundation for this larger research initiative.

The purpose of this project is to develop and test a patient survey to characterize the symptom experience, QoL and adherence to immunosuppressive medications in solid organ transplant recipients.

CHAPTER 3: STUDY OBJECTIVES

Objective 1: Identify and critically evaluate existing survey tools for assessing adverse symptoms of immunosuppression (ASI), quality of life (QoL), and adherence in transplant recipients. **(Tool identification)**

Objective 2: Develop a survey that gathers information about ASI, QoL, and adherence, as well as capturing clinical situation and patient demographics. **(Survey Development)**

Objective 3: Pilot the newly developed survey among a sample of individuals associated with the Canadian Transplant Association (CTA). **(Pilot Survey)**

Objective 4: Perform a descriptive analysis of the results of the electronic survey, and describe following results in frequencies and distributions. **(Descriptive Analysis)**

- Patient demographics:
    - age, gender, race, education, employment status, household income, marital status, province, proximity to transplant center
- Clinical situation of subjects:
    - type of transplant, time since transplant, number of visits to transplant center per year, immunosuppressive medications, doses per day, number of rejection episodes in the past 3 months, other medical conditions
- Symptom experience:
    - Prevalence of symptoms
    - Distress associated with symptoms
    - Symptom causal attribution (i.e. immunosuppression, other medications, medical conditions)
    - Self-perceived treatability of symptoms
- Adherence:
    - Overall adherence
    - Implementation and discontinuation
- Quality of Life:
    - Physical component summary
    - Mental component summary

Objective 5: Assess strengths and limitations of the survey tool, and feasibility for a multicenter study. **(Assess Feasibility)**

- Response rate
- Time required to complete survey
- Patient feedback
- Missingness of data

The methods and results section of this report will be organized according to the aforementioned objectives for clarity.

CHAPTER 4: METHODS

4.1 Ethical Consideration

Ethics approval for this project was obtained from the University of Saskatchewan Advisory Committee on Ethics in Behavioral Science on January 6, 2015. (Certificate of approval number 14-444).

4.2 Objective 1: Tool Identification

A comprehensive literature search was undertaken to identify existing validated questionnaires relating to symptom experience, quality of life and nonadherence to immunosuppressive medications. Quantitative tools that measured QoL, symptom experience or adherence in solid organ transplant recipients, and were published in English, were considered for review. Review articles, studies that used qualitative measures, studies that were specifically designed for use in a certain ethnic group, and studies that were not in English were excluded. A medical librarian provided guidance on the search strategy for this stage of the project. Three databases were searched, including Medline via Ovid SP, Psychinfo via Ovid SP, and EMBASE via Ovid SP. For the quality of life search, the Cumulative Index of Nursing and Allied Health Literature (CINAHL) (1969 through 2014) database was also included, since this resource has been known to index articles pertaining to this topic.

4.2.1 Quality of Life

The following search terms were used for the QoL literature search: [(Transplantation. mp.) and (exp Immunosuppressive Agents/ae [Adverse Effects] mp.) and (exp Quality of Life)] in Medline via Ovid SP; [(exp Organ Transplantation) and (exp Immunosuppressive Agent) and (exp Quality of Life)] in EMBASE via Ovid SP; [(exp "Side Effects (Drug)" / or Immunosuppressants. mp.) and (exp Quality of Life) and (Transplantation. mp.)] in Psychinfo via Ovid SP; [(MH "Immunosuppressive Agents+")ˆ and (MH "Quality of Life") and (MH "Organ Transplantation") or (MH "Heart Transplantation+") or (MH "Kidney Transplantation+") or (MH "Liver Transplantation") or (MH "Lung Transplantation+") or (MH "Pancreas Transplantation+")] in the Cumulative Index of Nursing and Allied Health Literature (CINAHL).

4.2.2 Symptom Experience

The literature search for tools to measure symptom experience in Medline via Ovid SP, EMBASE via Ovid SP, and Psychinfo via Ovid SP included the terms (organ transplantation/or

transplantation/or exp heart transplantation/or exp kidney transplantation/or exp liver transplantation/or exp lung transplantation/or exp pancreas transplantation/or exp spleen transplantation) and (exp immunosuppressive agent/) and ((symptom* adj4 (distress or experience* or occur*)).mp. [mp - title, abstract, original title, name of substance word, subject heading, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier].

4.2.3 Medication Adherence

The medication adherence search in the three databases (Medline via Ovid SP, EMBASE via Ovid SP, and Psychinfo via Ovid SP) consisted of the terms: (organ transplantation/or transplantation/or exp heart transplantation/or exp kidney transplantation/or exp liver transplantation or exp lung transplantation/or exp pancreas transplantation/or exp spleen transplantation) and (medication compliance/or exp patient compliance) and (exp immunosuppressive agent/).

4.3 Objective 2: Survey Development

It was determined that the survey would contain five sections: 1) demographic and clinical characteristics; 2) symptom experience; 3) quality of life; 4) adherence to immunosuppressive medications; and 5) comments.

The demographic questions section was included to assist in characterizing the population. A series of relevant demographic questions were drafted from the research team, and an additional expert in transplantation was consulted to review the questions for relevance in this population.

Tools to assess symptom experience, quality of life, as well as adherence, were generated from the literature search in objective one. Preference was given to instruments with proven validity in transplant populations, and instruments that were used to study different types of solid organ transplants (versus just one specific organ group), were comprehensive in quantifying symptom experience, QoL, or adherence to immunosuppressive medications and concise in nature. With respect to self-reported adherence, we aimed to identify a tool that accounted for both the number of doses taken as well as the timing of administration of immunosuppressive medications.

For symptom experience, there was the desire to comprehensively cover the occurrence and distress of the adverse symptoms, as well as including as many adverse symptoms as

possible. We also aimed to assess the patient's perception of causal attribution and treatability of the adverse symptoms experienced. Adapting causal attribution and treatability questions into the selected symptom experience tool was preferred rather than adding another tool, to minimize survey burden. With respect to quality of life and adherence, concise tools were also given preference since the patient experience section alone would be lengthy.

As is common practice in survey design,[38] an open-text comment box was added at the end of the questionnaire to collect additional details and feedback from the respondents. These comments were potentially important in this study since one of the objectives was to assess the feasibility of a future multi-center study.

4.4 Objective 3: Pilot Survey

4.4.1 Study Population

The questionnaire was sent to patients with a solid organ transplant who were members of the Canadian Transplant Association (CTA). The CTA is a national charitable organization with a mandate of raising awareness of organ and tissue donations.[39] Their membership consists of donor families, living donors and their relatives and friends, health care professionals, and approximately 249 transplant recipients. The transplant cohort includes recipients who have undergone a solid organ, tissue, or stem cell transplant. This group includes a diversity of solid organ transplant types (e.g. kidney, liver, multi-organ, etc.) widely geographically distributed across the country, which was ideal for the purposes of this pilot study. Correspondence with CTA executives revealed that the CTA members are active users of the association's website, and emails are the preferred form of communication, hence the link to the survey was distributed by email.

4.4.2 Questionnaire Distribution & Data Collection

An invitation to complete a questionnaire was emailed to the CTA membership list by the website administrator. Filter questions were included to specifically identify participants who have received a solid organ transplant, and to exclude pediatric patients. To minimize the survey length, and avoid unnecessary complexity, a survey platform with options for skipping questions and branching questions was needed. Various survey platforms were tested to assess their suitability for this questionnaire. The Research Electronic Data Capture (REDCap) survey tool hosted through the University of Saskatchewan was deemed the most appropriate platform for

this study.[40] In addition to meeting the requirements of unlimited skip logic and branching options, technical support for this software was easily accessible on campus.

The time required to fill out the survey was estimated to be between 30 and 45 minutes according to feedback after testing on laypersons. Although this may be viewed as lengthy, by way of this pilot we hoped to determine the appropriate balance between keeping the survey concise and covering the research topic in a comprehensive manner. In a systematic review of electronic surveys, Sheehan and colleagues analyzed 31 studies conducted between the years 1986-2000, resulting in an average response rate of 37%.[41] Assuming a high degree of patient buy-in to a topic likely of importance to them, we aimed to achieve a response rate of 40%.

Response rate is essential to the success of any survey. To encourage a high response rates, the Dillman Tailored Design method was utilized.[42] This method recommends communicating with the study population multiple times. An invitation is initially sent that explains the expected impact of the study and the importance of responses, and reminders are sent to non-responders-to encourage participation. The use of concise and simple wording is recommended in all communications. As recommended by Dillman and other survey experts,[42-44] we planned to send an advance email approximately one week prior to the survey distribution. Two reminder emails were also to be sent to potential participants consecutively, approximately one week after the email containing the actual survey link was received.

Participants were given the option to receive a $ 5 Tim Horton gift card as compensation for their time to fill the survey. If the respondent opted to accept the incentive, they were redirected to a separate survey to provide their contact details.

In order to preserve the anonymity of the respondents, the CTA executive was responsible for distributing the surveys to their members. In a deviation from accepted survey practices, the CTA executive claimed that sending too many emails in a short time frame could burden the members and provoke them to unsubscribe from the email distribution list. The emails were therefore consolidated and the interval between the emails was extended. Data collection occurred between April 20th, 2015 and May 26th, 2015 according to the following schedule:

- April 20th – Initial email sent to the entire mailing list of the CTA, including a cover letter and a link to the survey (Appendix 1).

- April 27th – First reminder email sent to the entire mailing list of the CTA, which contained a link to the survey (Appendix 2).
- May 20th – Second reminder email sent to the entire mailing list of the CTA, which contained the survey link (Appendix 3).
- May 26th – Data collection concluded.

Each questionnaire had a unique identification number, and all of the responses were saved on a password secured laptop that was maintained by the research team.

4.5 Objective 4: Descriptive Analysis

Data was directly imported from the REDCap survey platform into the Statistical Package for Social Sciences (SPSS 19.0 for Windows®). Statistical tests such as mean, median, range, frequency, and standard deviation were used to analyze patient demographics. The questionnaire consolidated three previously validated tools, each with a specific recommended analysis plan, hence statistical analysis was initially performed on each section separately.

The Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD-R59),[45] which was used to measure symptom experience, consisted of a large number of questions that are ordinal in nature. For the symptom occurrence questions, the responses were stratified according to gender, and the scores were summed and grouped into tertiles (highest, medium, lowest prevalence symptoms). Mean scores were calculated for the distress questions, which used a numerical Likert scale ranging from 'not distressing at all (0)' to 'terribly distressing (4)'. Mean calculations took into account the number of respondents reporting a certain value, as well as the distress value they selected (i.e., if two respondents scored 0 and one respondent scored 1, the denominator was three since this is the number of respondents that answered the distress question). Causal attribution and treatability questions were reported as the proportion of respondents who answered with 'strongly agree' or 'agree' to each question on a scale of 'strongly agree' to 'strongly disagree'.

The QoL assessment was conducted with the Short Form-12v2 (SF-12®). This analysis was carried out using the Quality Metric Health Outcomes® Scoring Software 4.5, which generated reports comparing the physical and mental health scores of the respondents to general populations, and compared eight items: physical functioning, physical role, general health perceptions, bodily pain, vitality, social functioning, emotional role and mental health. The software translated the values into norm-based values (with 50 equating to the US average ±

standard deviation of 10), to provide a better understanding of our sample compared to the general population (albeit, not Canadian), taking into consideration age and gender norms.

The BAASIS© [46] tool measured patients' implementation and discontinuation phases of immunosuppressive medications in the last four weeks across four questions using a 6-point Likert scale ranging from 'never (0)' to 'every day (5)'. The implementation phase refers to the patient's ability to take the medications according to the prescribed regimen, at the correct time, without missing doses, while the discontinuation phase refers to whether the patient stopped taking their medications. A 'yes' answer to any of the first three questions indicated an issue in implementation, while a 'yes' answer to question four indicated a discontinuation of immunosuppressive medications. Overall adherence was captured as a dichotomous variable, combining answers from both implementation and discontinuation questions. A 'no' response on all questions (1a, 1b, 2, 3, and 4) indicated overall adherence, while a 'yes' response on any of the questions (1a, 1b, 2, 3, and 4) was considered non-adherent. Overall adherence was also captured as a continuous variable, with respondents reporting adherence to immunosuppressive medications over the last 4 weeks on a visual analog scale (VAS), in which higher scores represented higher overall adherence.

4.6 Objective 5: Assess Feasibility

To assess the feasibility of examining of symptom experience, quality of life and nonadherence in a single survey tool, the following aspects were taken into consideration: response rate, time required to complete survey, missing data, patient feedback.

Response rate was calculated by dividing the number of respondents who filled the survey completely (demographics and clinical, symptom experience, quality of life and adherence to immunosuppressive medications) by the total sample. Patients who did not provide a response on all questions were defined as partial responders. The electronic platform did not have the capability of capturing the time required to complete the survey, because respondents could complete the survey in more than one session (i.e. start the survey, save their answers and then restart from where they stopped last time). The research team opted to use this approach since they believed it would positively impact on completion rate. Missing data was calculated separately for each patient, based on the differing item response characteristics of each survey. This approach was necessary since each respondent had a different number of total questions (based on immunosuppressive medication choices and symptoms reported).

Qualitative patient feedback was also captured to gain insight into the perspectives of respondents regarding the survey topic and/or survey itself. Thematic analysis was used to identify common themes from patient's comments. This involved compiling the responses and reviewing the data, labeling or coding the data, identifying initial patterns or themes in the responses, reviewing the themes and then defining and naming the themes, and summarizing them in this report. This process was undertaken by hand initially by S.A., and then reviewed by H.M.

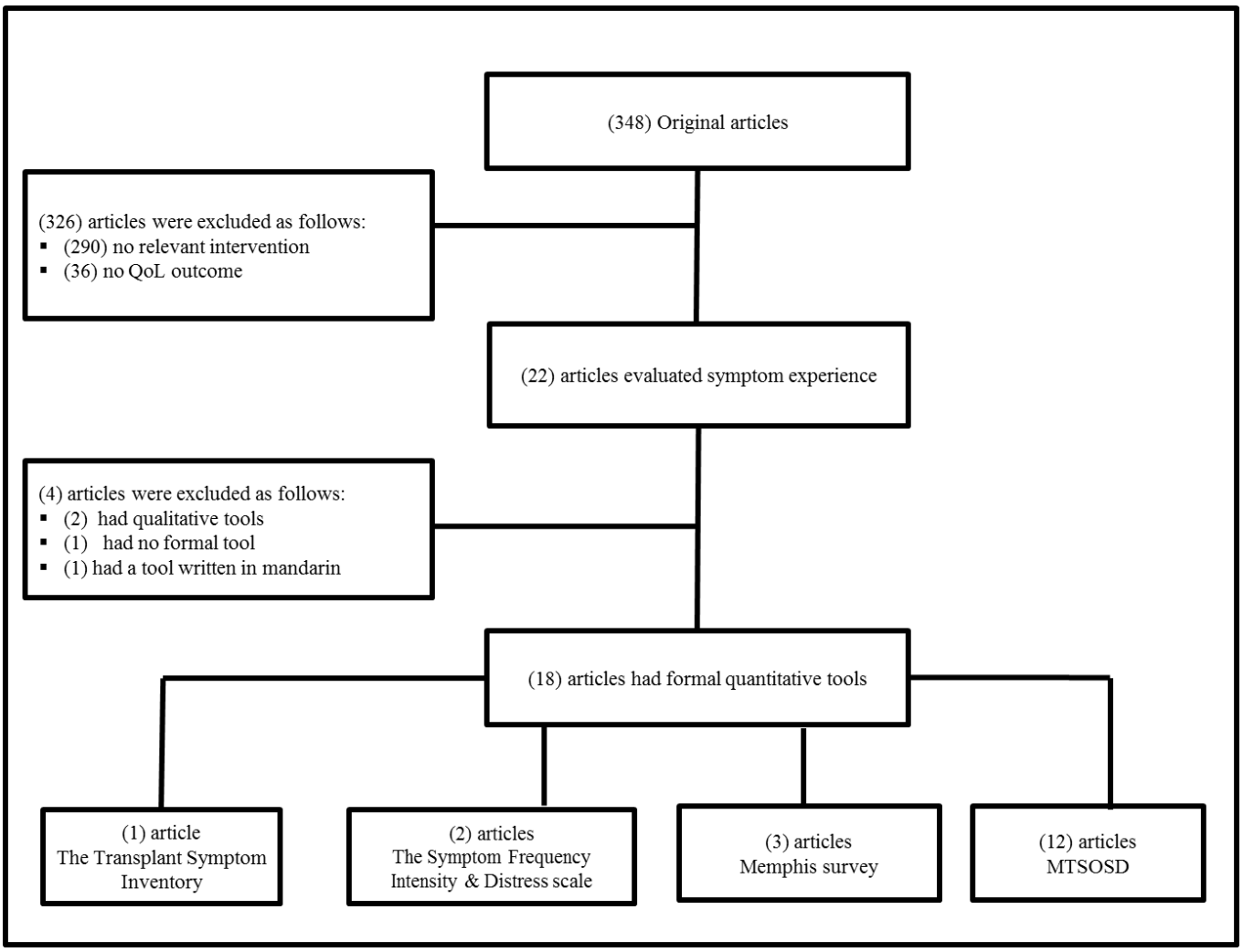
CHAPTER 5: RESULTS

5.1 Objective 1: Tool Identification

5.1.1 Symptom Experience

The systematic literature search for symptom experience generated 348 original articles (Figure 1). Twenty-two articles emerged as relevant, and four separate tools were reviewed.

Figure 1. Summary of the search strategy to identify articles pertaining to symptom experiences in patients with solid organ transplants



- **Modified Transplant Symptom Occurrence and Symptom Distress (MTSOSD)**

The MTSOSD scale is a self-administered questionnaire designed to measure symptom occurrence rated on a five-point scale from 'never occurring (0)' to 'always occurring (4)', and symptom distress from 'not at all distressing (0)' to 'extremely distressing (4)'. The original tool was designed to be used in heart transplant recipients and assessed the occurrence and distress of 27 immunosuppression adverse symptoms on a Likert scale.[47] The questionnaire has since been modified to include a total of 59 symptoms, to be inclusive of other types of organ transplants, and newer immunosuppressive medications.

A study aimed at updating and validating the 59 items in the MTSOSD scale was carried out in 24 renal and 84 lung transplant patients. Pilot testing was conducted on the renal transplant recipients to measure the clarity of the questions and the participants' comprehension of the questions. The questionnaire was modified according to this feedback and tested again in the lung transplant group. Discriminant validity was tested by comparing symptom experience between men and women, and also between patients with and without depressive symptoms. Women reported a significantly higher level of symptom distress compared to men ($p = 0.0017$), and also a tendency towards a higher symptom occurrence compared to men. Patients with depressive symptoms reported a higher symptom occurrence ($p = 0.030$) and a higher symptom distress ($p = 0.006$) compared to those with no depressive symptoms.[45]

Two other studies aimed to validate the MTSOSD tool. The first study was conducted on 113 renal transplant recipients in Belgium.[48] Content validity was tested by a thorough review of the literature, and an experts' review (consisting of two clinical nurses, two nephrologists, and two cardiologists). Construct validity was assessed from transplant literature reporting that symptom occurrence and distress are correlated with depression, and that women experience more adverse symptoms and distress than men. The results obtained from this study were consistent with these assumptions, as both symptom occurrence and distress were correlated with depression and symptom distress and depression were correlated using (Spearman coefficient ($r = 0.32$ and $r = 0.54$; $p < 0.001$, respectively). Women expressed higher scores for symptom occurrence and distress compared to men ($p < 0.001$). Finally, discriminant validity was evaluated by comparing the transplant recipients to a healthy control group, in which the transplant recipients reported significantly higher scores for symptom occurrence and symptom distress ($p < 0.00001$).[48]

The second validation study adapted a translated version of the questionnaire in Turkish to 180 liver and kidney transplant recipients.[49] The content validity index showed an ideal score of 1.0 according to 13 expert reviewers, indicating that it accurately measures knowledge of adverse symptoms occurrence and distress. Construct validity was confirmed in 30 liver transplant recipients, where women reported a higher symptom frequency and more symptom distress than men ($p < 0.01$). Higher symptom occurrence and more distress also occurred in participants who reported high depressive values compared to participants who reported low depressive values ($p < 0.001$). The Spearman-Brown coefficient was 0.991 for symptom occurrence and 0.992 for symptom distress, which suggests that occurrence and distress were correlated.[49]

The MTSOSD has been used in several studies in kidney and liver transplant populations to assess relationships between symptom experience and adherence. A study in Taiwan investigated the relationship between symptom experience and side effects on immunosuppressive medications, and effect on treatment adherence among 412 kidney transplant recipients.[50] In another study conducted in Belgium, the MTSOSD was used to evaluate quality of life, treatment adherence, and patient and parent perceptions of adverse symptoms in 23 adolescent renal transplant recipients.[15] The MTSOSD scale was also used to assess symptom experience, and to study the relationship between symptom experience and immunosuppressive medication nonadherence in 123 liver adult transplant recipients,[16] and 239 kidney transplant recipients.[51] A final study explored adverse effects of immunosuppressive medication and their relation to symptom experience in 356 kidney transplant recipients on maintenance immunosuppressive therapy.[14]

Heart transplant studies have used the MTSOSD as well. The MTSOSD assessed symptom experience related to adverse symptoms of immunosuppressive medications in 105 such patients, finding that hair growth was the most prevalent symptom in both women and men.[47] In another study of 261 German heart transplant recipients, the most prevalent symptoms were tiredness, lack of energy, and nervousness.[30]

The MTSOSD tool has also been used to study the effect of specific immunosuppressive agents on symptom experience. In a study of 666 kidney transplant recipients, the interrelation between kidney function, quality of life, and adverse symptoms of immunosuppressive medications was investigated, along with the impact of belatacept and cyclosporine. [52]

- **Memphis Survey**

The Memphis Survey was developed and psychometrically validated at the University of Tennessee. It consists of 107 items and measures the presence of adverse symptoms of immunosuppression and how troubling they are to the individual on a five-point scale from 'not at all (0)' to 'all the time or extremely troubling (4)'. The tool was pilot tested for clarity and content among 13 kidney transplant recipients.[53] Following this, it was tested for internal consistency in an American study of heart, kidney, kidney-pancreas and liver transplant recipients (n=505) (Cronbach alpha>0.8).[54] A third study used the Memphis survey to evaluate immunosuppression-related side effects in 722 solid organ transplant recipients (heart, kidney, liver, lung, pancreas and intestine) in the United States.[55]

- **The Symptom Frequency Intensity and Distress scale:**

The original tool was designed in 1978 to assess symptom distress in chronic medical conditions. It included 10 symptoms (nausea, mood, appetite, insomnia, pain, mobility, fatigue, bowel pattern, concentration and appearance). Fifty-three cancer patients tested the tool and showed acceptable consistency (coefficient alpha= 0.82, standardized alpha=0.83).[56] The scale was subsequently modified in a Swedish study to evaluate health related QoL in 25 stem cell transplant recipients.[57] The new version includes 25 items and measures symptom frequency on a four-point scale from 'no, not at all (0)' to 'yes, very much (3)'. It also measures the intensity and the impact of symptoms on daily life (0=no impact to 3=great impact). One question in the survey asks the patient to rate perceived general health, using the response scale 0=excellent to 3=poor.[57] The following symptoms are investigated on this questionnaire: nausea, vomiting, fever, shivering, cough, pain, breathing, tiredness, dry mouth, sore mouth and throat, changes of taste, diarrhea, constipation, skin problems, poor appetite, sleep problems, ambulation problems, eye problems, depression, anxiety, difficulties in concentrating, forgetfulness, hair loss, sexual problems and change of appearance.

- **The Transplant Symptom Inventory:**

The Transplant Symptom Inventory was developed in the United States to assess patient symptoms before and during the first year of transplant and was tested in 85 lung transplant recipients.[31] Consisting of 64 items, it measures symptom frequency and distress using a 5-point Likert scale. Subjects rate how frequently each symptom occurs from 'never (0)' to 'always (4)', and then rate how distressing each symptom is from 'never (0)' to 'extremely (4)'. A committee

of five experts (three nurse practitioners and two lung transplant physicians) confirmed content validity from previous literature and their clinical experience. Cronbach's alpha for symptom occurrence was 0.912 and 0.962 for symptom distress, indicating excellent internal consistency of the questionnaire.[31]

Summary:

Preference was given to validated instruments that assessed as many adverse effects of immunosuppressive medications as possible, covered the two dimensions of symptom experience (occurrence and distress) and were widely used in transplant populations. The MTSOSD-59 version was determined to best match these criteria, and was chosen over the Transplant Symptom inventory because it had been used in more organ populations and had more studies to support its validity.

5.1.2 Quality of Life

The initial search assessing QoL in transplant recipients generated 349 articles. Of these, 41 articles containing 21 instruments were identified in the systematic search assessing QoL in transplant recipients. Eighteen tools were eliminated due to their specificity and focus on specific area/s of QoL rather than a comprehensive tool that measures overall QoL in adult transplant recipients (Table 1).

Table 1. Eliminated quality of life instruments and rationale

QoL Tools	Focus
The Gastrointestinal Symptom Rating Scale (GRSR)	Gastrointestinal associated common symptoms.[58-62]
Gastrointestinal Quality of Life Index (GIQLI)	Gastrointestinal specific health related QoL.[61,62]
The Brief COPE	Different coping dimensions to transplant.[63]
The Social Support Scale (SSS)	Social support provided to the individual by the people in their lives (i.e. family, friend,
The Personal Resource Questionnaire (PRQ2000)	Perceived level of social support.[63]

QoL Tools	Focus
The Psychosocial Adjustment to Illness Scale (PAIS)	Additional psychosocial dimensions of health-related QoL.[65]
The Child Health Questionnaire (CHQ)	Children and young people aged 4-18 years.[35]
The Objective Karnofsky Performance Status	Intensity of treatment and ability of the patients to take care of themselves.[65]
The Baecke Scale	Physical activity at work, during leisure time, and sports during leisure time.[5]
The Beck Depression Inventory	Patients' depressive symptoms.[5,66-69]
Stat and Trait Anxiety Inventories Y1 and Y2 (STAI)	Anxiety.[70]
the Psychological General Well-Being Index (PGWBI)	Psychological health and well-being.[62,70]
The Life Satisfaction Index (LSI)	General feelings of well-being.[33,71,72]
The Perceived Health and Competence scale	Perceived self-efficacy relevant to health in general.[63]
The Quality of Life index tool Kidney transplant version 3	Satisfaction and importance of various domains to kidney transplant recipients.[64]
The Sickness Impact Profile (SIP)	Health problems interference with daily activities and behaviours.[73]
Nottingham Health Profile scale (NHP)	Subjective health status.[74]

After eliminating the above instruments for the aforementioned reasons, three tools were considered: The Short Form 36, the Short Form 12, and the Euroqol.

- **Short Form 36 (SF-36):**

The SF-36 is one of the most widely used health related QoL scales. It consists of 36 items and covers eight subscales, which measure health concepts in the following dimensions: physical functioning, physical health, bodily pain, general health, vitality, social functioning, emotional and mental health. It has been used in various solid organ transplant populations (lung, kidney, heart and liver).[5,52,58,65,67-69,75-85] Data from the Medical Outcome Study (MOS)[86] were used to test the SF-36's clinical validity. Correlation of clinical tests of validity were compared. Three-quarters (74%) of patients with serious medical and depression conditions reported their health as poor. However, nearly half (44%) of patients with serious medical conditions and 22% of patients with minor medical or depressive conditions reported poor health.[82] A comparison of the SF-36 scores in healthy individuals, and other chronically ill populations is available for many countries.[86]

- **Short Form 12 (SF-12):**

The SF-12 is a validated short version of the SF-36. It consists of two items for each of the domains of physical functioning, emotional, general health and mental health, and one item for the domains of bodily pain, general health, vitality and social functioning. The eight subscales are aggregated into two component summaries, the physical component score (PCS) and the mental component summary (MCS). Each domain is scored on a scale of 0 to 100, with 0 and 100 representing worst and best QoL, respectively. The SF-12 software compares individual scores to the adjusted norm-based values of a US healthy individual (with a score of 50 equating to the US average ± standard deviation of 10). Mid point of 50 indicates average health comparable to norm values.

Criterion-related validity was confirmed in a study conducted on 44395 dialysis patients in 2006, which compared scores of the SF-36 to scores of the SF-12. A high correlation coefficient was obtained between the two tools ($r=0.94$ for PCS and MCS subscales, $p<0.0001$).[87]

The SF-12 has been used in several transplant cohorts. In one study of liver transplant recipients (n=126) quality of life was assessed in relation to unemployment,[88] while in another liver cohort (n=31) quality of life was compared before and after modifying immunosuppressive medications (by switching mycophenolate mofetil to enteric coated mycophenolate sodium).[60] A study of multi-organ transplant recipients (n=722) used SF-12 to compare differences in quality of life according to transplanted organ, based on time since transplant and different immunosuppressive medication protocols.[55] Another study used SF-12 in kidney transplant

recipients (n=231) to measure differences in quality of life for patients with different immunosuppressive medications (cyclosporine vs. tacrolimus vs. experience with cyclosporine and tacrolimus).[89] The tool was used in liver transplant recipients (n=36) to evaluate quality of life after 20 years or more of transplant).[90]

- **Euroqol (EQ-5D):**

The EQ-5D consists of two sections. The first section involves five items to assess the patient's level of functioning, while the second is a 20 cm visual analog scale, in which the patients are asked to rate their health on the day they are filling out the survey.[5,91,92] Validity was tested in a random sample (n=1980) of patients obtained from two clinic registries in the UK. Those who had a medical problem and/or a chronic disease reported more problems compared to a matched healthy sample on all of items on the EQ-5D (ability to visit the doctor clinic, self-care, main activity, leisure activity, pain/discomfort and depression/anxiety) ($p<0.05$) indicating construct validity. Discriminant validity was examined by comparing the EQ-5D scores to the SF-36 scores for the total population. Agreement in scores was noted between the scales, with EQ-5D and SF-36 Spearman's rank correlation coefficient ranging from 0.48-0.6 ($p<0.01$), It is worth mentioning that EQ-5D has been reported to be less sensitive compared to the SF-36 in three of the response categories.[93]

Summary:

Since preference was given to validated and previously used tools in transplant populations, this narrowed the choice to SF-36, and SF-12. The SF-12 was determined to be the most suitable instrument to be used in this project, primarily due to its brevity. Since QoL was only one of three areas to be explored, a brief, yet comprehensive tool was required to keep the survey to a reasonable length.[87]

5.1.3 Medication Adherence

Adherence to immunosuppressive medication was the focus of 323 articles. Of these 32 articles and seven quantitative tools were identified, two tools were eliminated due to their specificity for certain populations (pediatrics) and one tools was eliminated as it was written in Japanese. Four tools that were selected for further review were:

- **Medication Adherence Report Scale (MARS):**

The MARS consists of two questions reflecting unintentional nonadherence (e.g. forgot to take my medications), and three questions on intentional nonadherence (e.g. deliberate decision to skip a dose). Questions are rated on a 5-point Likert type scale encompassing 'strongly agree to strongly disagree'. MARS was validated in a study of liver transplant recipients (n=444) that compared three different measures of nonadherence (immunosuppressive medications blood levels, physician reported adherence, and patient self–reported adherence) using patient medical charts between the years of 2003 and 2009. Convergent validity was evident as physician reported rates of nonadherence were associated with self-reported nonadherence (Odds ratio: 2.5, p=0.03), as well as tacrolimus blood levels variations from a specified clinical target, which was set to be 100-350 ng/ml for cyclosporine and 6-10 ng/ml for tacrolimus (r= 0.43, p=0.03 R^2 = 0.015).[94] The MARS was also used in a study that aimed to explore differences in intentional and nonintentional nonadherence to immunosuppressive medications in 218 kidney transplant recipients in London.[66]

- **Immunosuppressant Therapy Adherence Scale (ITAS):**

The ITAS is a 4-item questionnaire that asks respondents how frequently they behaved in terms of forgetfulness, carelessness, and cessation of immunosuppressive medications as a result of the adverse symptoms experienced in the previous three months. Answers are rated on a 4-point Likert-type scale as follows: 3=0% (none of the time), 2=1-20%, 1=21-50%, and 0=greater than 50% of the time (very frequent). Scores of ITAS can range from (0) poor adherence to (12) perfect adherence.

Validity of the ITAS was examined in three studies. The first study was conducted by Chisholm (the developer of the ITAS scale) in a population of (n=222) kidney transplant recipients.[95] Self-reported scores were significantly correlated with that of serum creatinine and serum concentration of immunosuppressive medications ($p<0.01$), indicating convergent validity. An acceptable internal consistency was also achieved (Cronbach's alpha=0.81).[95] The second study involved 137 kidney transplant recipients. The adherence rate (65%) calculated by the ITAS was consistent to the adherence rate obtained through refill records (63%), which was evidence for convergent validity.[96] The third study aimed to evaluate the psychometric properties among 141 solid organ transplant recipients. Scores of the ITAS were significantly associated to scores from tools used to assess social support and adaptability ($r \geq 0.2$, $p<0.05$), indicating

construct validity. Cronbach's alpha was 0.87-and the Guttman split-half coefficient was 0.9, indicating good internal consistency and reliability, respectively.[97]

The ITAS was used to determine adherence in a sample of 556 solid organ transplant recipients. In this study of kidney, liver and other transplants, just over half (58%) of the population was shown to be adherent to their immunosuppressive medications (ITAS total score of 12).[32] The tool was also used to assess differences in adherence in kidney transplant recipients (n=808) between two immunosuppressant regimens (enteric coated mycophenolate sodium vs. mycophenolate mofetil). [98] In a study of 744 kidney transplant recipients, the ITAS was used to measure adherence during the first year after transplant. Nonadherence rates peaked at the end of the third month and then plateaued for the next nine months.[99] A study of 512 kidney transplant recipients explored the relationship between adherence to immunosuppressive medications, as well as barriers to adherence and life satisfaction. Nonadherent recipients (177/512) scored higher on the immunosuppressant therapy barrier scale than adherent recipients ($p<0.001$). Nonadherent patients also had lower life satisfaction scores than the adherent ones ($p < 0.001$).[100] In a study investigating the relationship between social support and adherence to immunosuppressive medications, 81 kidney transplant recipients reported a significant correlation between social support and adherence (correlation coefficient=0.214, $p<0.05$).[101] The tool was also used to measure differences in adherence to immunosuppressive medications based on patient perceptions of benefit, and the impact of those beliefs on symptom experience (n=326).[102]

- **Basel Assessment of Adherence with Immunosuppressive Medication Scale (BAASIS):**

There are two versions of the BAASIS. The interview questionnaire is conducted by a health care professional, while the paper version of the questionnaire is self-reported by the patient. Both versions contain the same questions, with slightly different wording. This scale is composed of four items that quantify taking and timing of medication, drug holidays, and dose reductions.

The translated English version of the questionnaire was validated in a study of 100 kidney transplant patients in Brazil. Cronbach's alpha indicated an acceptable internal consistency of 0.7. A convenience sample of 21 members of the original population was used to examine the test-retest reliability, reporting high agreement (95.2%) and a Kappa coefficient of

0.88. Revisions recommended by a committee of experts and feedback from a sample of patients was used to finalize the tool and assess content validity. The final version of the tool was assessed for criterion validity (Spearman's correlation coefficient 0.65, $p<0.001$). [103]

The BAASIS was used in a study conducted among different types of solid organ transplant recipients (79 heart, 55 liver, 104 lung) in Belgium, to assess self-reported immunosuppressive medications nonadherence, along with electronic monitoring and tacrolimus blood assays. Interestingly, rates of nonadherence were found to be higher with the self-reported measure compared to electronic monitoring and assay values.[104] A group of 1505 solid organ transplant recipients (kidney, liver, lung and heart) also used the BAASIS to report pre-and post-transplant nonadherence.[105]

A variety of kidney transplant studies have used the BAASIS to assess adherence. It was used in a study in the Netherlands to explore the effect of goal cognition, illness and treatment perception on adherence 6 months after renal transplant (n=113).[106] Another study used the tool to compare three different ways of measuring nonadherence (self-report, physicians' assessment and immunosuppressive medications blood levels) in 241 kidney transplant recipients.[107] The relationship between nonadherence to immunosuppressive medications and patient perceptions was explored in another study of 212 kidney recipients. This study showed that recipients who believed their medication was important were more adherent with their medications.[108] Nonadherence to immunosuppressive medications and daytime sleepiness were studied in 926 kidney transplant recipients. A significant association between sleepiness and nonadherence was reported ($p<0.001$).[109] Finally, the BAASIS was used in a population of adolescent renal transplant recipients (n=62). Approximately two thirds of the population (65%) reported nonadherence in the last four weeks of taking immunosuppressive medications.[110]

A few studies have also used the BAASIS in heart transplant cohorts. A secondary analysis of the BRIGHT study evaluated nonadherence to immunosuppressive medications in 37 transplant centers in 11 countries (n=902), where respondents reported an overall nonadherence of 36%.[111] A pilot study of heart transplant recipients (n=50) used the tool to measure nonadherence differences after simplifying the medication regimen (twice daily CNI vs. once daily modified release tacrolimus). A decrease in nonadherent behavior was associated with regimen simplification [112] A follow up study that involved 72 heart transplant recipients showed

similar results. Nonadherence at baseline was 75%, while at eight months it decreased to 40% ($p<0.0001$).[113]

- **Morisky Medication Adherence Scale (MMAS-4):**

This scale consists of 4 measures of nonadherence: Patients 1) forgot taking their immunosuppressive medications, 2) were careless about taking their immunosuppressive medications, 3) discontinued immunosuppressive medications due to feeling better, or 4) discontinued immunosuppressive medications due to feeling worse. An answer of 'yes' to any of those items indicates nonadherence.

Criterion validity of this tool was explored by comparing its results to immunosuppressive blood levels variation among 209 renal transplant recipients in China. Adherence scores measured by this scale were significantly associated with immunosuppressive medications blood levels ($p< 0.001$) and good internal consistency was reported (Cronbach's alpha=0.703).[114]

The MMAS-4 was used in three additional studies to assess adherence. In a study of heart transplant recipients (n=99), 33% reported nonadherence to immunosuppressive medications.[115] A cohort of kidney transplant recipients (n=312) showed an increase in nonadherence over time using the MMAS-4.[116] Finally, the MMAS-4 was used in a study of liver transplant recipients (n=65) to assess whether adherence varied with two immunosuppressive regimens. [117]

Summary:

Preference was given to tools that were widely used in transplant literature, assessed different areas of nonadherence to immunosuppressive medications (medications intake, administration, regularity of drug intake, presence of drug holidays). The BAASIS was chosen for this project, as it was the only tool that assessed both taking and timing of immunosuppressive medications.

5.2 Objective 2: Survey Development

Five major domains of information were deemed necessary for this questionnaire, demographics and clinical characteristics, symptom experience, quality of life, adherence to immunosuppressive medications and comments. Thus, these sections were developed independently before merging into one single tool.

5.2.1 Demographics

Two filter questions were included to ensure the target population (i.e., adult solid organ transplant recipients) was responding to the survey. Standard socioeconomic status questions

were included to describe age, gender, ethnicity, education, employment, family income, marital status, and province of residence. Transplant specific questions were included to characterize the transplant and assess comorbidities and disease stability, such as type and year of transplant, medication regimen and frequency, incidence of transplant rejection, other medical conditions experienced, and kidney function.

5.2.2 Symptom Experience

The MTSOSD-59 version was incorporated into the questionnaire to measure symptom experience. This tool measures the frequency and distress of 59 adverse symptoms potentially associated with immunosuppressive medications. Female/male versions differ in item nine: Painful menstruation/impotence. In addition, a 60th symptom (heartburn) was included, as it was identified to be a common adverse symptom in transplant recipients by the research team. At the end of the 60th item, respondents were given the option of reporting two additional adverse symptoms that they might have experienced-that were not included in the questionnaire.

Each question asked the respondent about the occurrence, the distress, and the perceived cause of the adverse effect, including immunosuppressive medications, other medications or underlying medical conditions. Respondents were given the choice along a continuum of 'never' to 'always' for symptom occurrence. If they chose anything but never (i.e., occasionally, regularly, almost always or always) they would be directed to rate their symptom distress on a scale from 'not distressing at all (0)' to 'terribly distressing (4)'. Next, questions were specifically asked based on which immunosuppressive medications were reported in the demographic section of the questionnaire. For instance, if the respondent chose sirolimus as part of their immunosuppressive regimen, they were asked whether they believed sirolimus was causing the adverse symptom. Distress, cause, and treatability sequence questions were prompted for each adverse symptom. Respondents reported cause and perceived treatability of each potential adverse symptom on a Likert scale of 'strongly agree' to 'strongly disagree'.

5.2.3 Quality of Life

The SF-12 was compiled into the questionnaire to measure QoL. The SF-12 software compares individual scores to the adjusted norm-based values of a US healthy individual (with a score of 50 equating to the US average ± standard deviation of 10). Physical and mental component summary scores can range between 0 to 100, indicating worst and best health status, respectively. Mid point of 50 indicates average health comparable to norm values.

5.2.4 Adherence to Immunosuppressive Medications

The BAASIS was used in the fourth section of the questionnaire to evaluate adherence to taking into account both implementation and discontinuation, and a visual analog scale ranging from '(0) no adherence' to '(100) perfect adherence'.

5.2.5 Instrument Pre-testing

After developing the initial draft of the survey, members of the advisory committee and a transplant physician reviewed the questionnaire. Modifications were made to the questionnaire accordingly. Since the questionnaire consisted of previously validated tools to measure QoL, symptom experience and adherence, further testing in a transplant cohort was not required. The final electronic survey was tested on 10 laypeople using the survey platform, to confirm the functionality of the questions.

REDCap survey platform has a limited forcing function capability, which displays a general message informing the respondent that they have missed a question. The message however, does not specify which specific question(s) were missed and does not prevent the respondent from proceeding to answer further questions. Therefore, respondents might have had missed answering some of the questions due to the survey length and the ambiguity of missed questions message or because they chose not to answer.

5.3 Objective 3: Survey Pilot

5.3.1 Response Rate

The advance letter including the link to the survey was sent to 249 solid organ transplant recipient members of CTA. When the data collection period closed, a total of 127 questionnaires were received, resulting in a response rate of 51%. Fourteen participants did not fill out the SF-12 or the BAASIS, while two respondents did not answer any of the BAASIS items. The remaining 111 participants (45 % of the entire population surveyed) completed the entire survey. The partially completed questionnaires were included in the analysis since the three tools used in this study (MTSOSD, SF-12, and BAASIS) each had a specific scoring and analysis recommendation.

5.4 Objective 4: Descriptive Analysis

5.4.1 Demographics of Respondents

The sample consisted of 71 (56%) males, and 56 (44%) females (Table 2). The average age of respondents was 55.5, ranging from 21 to 81 years. Most participants (85%) completed

some form of education after high school. The majority of the population (71%) was of European descent. Respondents were most commonly in a household income bracket of $40,000 – 60,000 per year (20%), with only 4% reporting household incomes of less than $20,000. Most participants (76%) were married or in a common in law relationship.

Table 2. Patient demographics

Characteristic	**Total Population**		**Men**		**Women**	
	Count	%	Count	%	Count	%
Gender	127	100	71	55.9	56	44.1
Age	Mean ± SD 55.5 ± 13.2		Mean ± SD 59.8 ± 11.8		Mean ± SD 50.0 ± 13.0	
Education						
▪ Grade 8 or less	1	0.8	1	1.4	0	0.0
▪ Some high school	5	3.9	4	5.6	1	1.8
▪ High school diploma	13	10.3	8	11.3	5	8.9
▪ Registered apprenticeship	17	13.4	7	9.9	10	17.9
▪ General & vocational college	44	34.6	25	35.2	19	33.9
▪ University certificate	33	26.0	16	22.5	17	30.4
▪ Bachelor's degree	14	11.0	10	14.1	4	7.1
Ethnicity						
▪ Aboriginal	4	3.2	4	5.6	0	0.0
▪ Asian/South East Asian	2	1.6	1	1.4	1	1.8
▪ South Asian	1	0.8	1	1.4	0	0.0
▪ European	90	70.9	51	71.8	39	69.6
▪ West Indian/Caribbean	1	0.8	1	1.4	0	0.0
▪ Other	26	20.5	12	16.9	14	25.0
▪ Unknown	3	2.4	1	1.4	2	3.6

Characteristic	Total Population		Men		Women	
	Count	%	Count	%	Count	%
Employment						
▪ Employed (full Time)	40	31.5	22	31.0	18	32.1
▪ Employed (part Time)	12	9.5	6	8.5	6	10.7
▪ Unemployed/looking	1	0.8	1	1.4	0	0.0
▪ Unemployed/not looking	4	3.1	1	1.4	3	5.4
▪ Retired/pensioner	43	33.9	33	46.5	10	17.9
▪ Homemaker	4	3.2	0	0.0	4	7.1
▪ Student	4	3.1	1	1.4	3	5.4
▪ Not in work force	19	15.0	7	9.9	12	21.4
Income ($)						
▪ Less than 20,000	5	3.9	4	5.6	1	1.8
▪ 20,000 - 40,000	15	11.8	8	11.3	7	12.5
▪ 40,000 – 60,000	25	19.7	11	15.5	14	25.0
▪ 60,000 – 80,000	20	15.7	10	14.1	10	17.9
▪ 80,000 – 100,000	11	8.7	7	9.9	4	7.1
▪ 100,000 – 150,000	16	12.6	11	15.5	5	8.9
▪ 150,000 and above	16	12.6	10	14.1	6	10.7
▪ Prefer not to answer	19	15.0	10	14.1	9	16.1
Marital Status						
▪ Unmarried	17	13.4	5	7.0	12	21.4
▪ Married/common law	96	75.6	61	85.9	35	62.5
▪ Divorced/widowed/separated	14	11.0	5	7.0	9	16.1
Province of Residence						
▪ British Columbia	19	15.0	12	16.9	7	12.5
▪ Alberta	29	22.8	13	18.3	16	28.6
▪ Saskatchewan	15	11.8	14	19.7	1	1.8
▪ Manitoba	1	0.8	1	1.4	0	0.0
▪ Ontario	45	35.0	19	26.7	26	46.0
▪ Québec city	10	7.9	6	8.5	4	7.0
▪ New Brunswick	6	4.7	5	7.0	1	1.8
▪ Nova Scotia	2	1.6	1	1.4	1	1.8

5.4.2 Clinical Characteristics

About a third (33%) of respondents reported receiving a liver transplant, while nearly a quarter received a kidney or a heart transplant (23%, and 22%, respectively) (Table 3). More than half of the respondents (61%) received their transplant over 6 years ago. The majority of respondents (61%) lived at least an hour's driving time from their transplant center, and 28%

visited their transplant center twice a year compared to 33% who reported one or no visits per year.

With respect to immunosuppressant therapy, 91% (115/127) of respondents were on a calcineurin inhibitor, and just over half were on a mycophenolic acid derivative, 55% (70/127) and prednisone, 51% (65/127). Of the transplant recipients who were taking calcineurin inhibitors, 65% (75/115) were on tacrolimus immediate release, and 12% (14/115) were on tacrolimus extended release, while an additional 23% (26/115) took cyclosporine. Of the respondents who were on a mycophenolic acid derivative, the majority (69%, 48/70) were taking mycophenolate mofetil, while 31% (22/70) took enteric-coated mycophenolate sodium. Other medications that were reported by the cohort included azathioprine 17% (22/127), followed by sirolimus 8% (10/127) everolimus 2% (2/127) and leflunomide (1/127). In addition to taking immunosuppressant medications, respondents reported an average of seven (±4.8) other medications per day.

The majority of recipients (95%) reported that they had not been treated for transplant rejection, and felt that they had very good function of their transplanted organ (86%). The number of additional medical conditions ranged from 0-6 per respondent, with high blood pressure being the most common (reported by 48%). Fifteen percent of the population reported no other medical conditions. (Table 3).

Table 3. Clinical characteristics

Characteristics	**Total Population**		**Men**		**Women**	
	Count	%	Count	%	Count	%
Organ Transplant Type						
▪ Kidney	29	22.8	14	19.7	15	26.8
▪ Liver	42	33.1	23	32.4	19	33.9
▪ Heart	28	22.1	19	26.7	9	16.1
▪ Lung	22	17.3	15	21.0	7	12.5
▪ Multi-Organ	6	4.7	0	0.0	6	10.7
Time to Transplant Center						
▪ Within 1 hr Driving	78	61.4	50	70.4	28	50.0
▪ Within 3 hr Driving	29	22.8	12	16.9	17	30.4
▪ Within 5 hr Driving	10	7.9	4	5.6	6	10.7
▪ Greater than 5 hr	6	4.7	4	5.6	2	3.6
▪ Other	4	3.1	1	1.4	3	5.4

Characteristics	Total Population		Men		Women	
	Count	%	Count	%	Count	%
Number of Visits to Transplant Center per Year						
▪ Less than once per year	12	9.4	8	11.3	4	7.1
▪ Once	30	23.6	16	22.5	14	25.0
▪ Twice	36	28.3	19	26.8	17	30.4
▪ Three times	12	9.4	10	14.1	2	3.6
▪ Four times	20	15.7	9	12.7	11	19.6
▪ Five – six times	10	7.9	3	4.2	7	12.5
▪ More than six times	7	5.5	6	8.5	1	1.8
Time Since Transplant						
▪ Less than three months ago	1	0.8	0	0.0	1	1.8
▪ Six months – one year ago	1	0.8	1	1.4	0	0.0
▪ One- three years ago	10	7.9	4	5.6	6	10.7
▪ Three- six years ago	37	29.0	19	26.8	18	32.0
▪ More than six years ago	78	61.4	47	66.2	31	55.4
Immunosuppressive Medications*						
▪ Prednisone	65	51.0	36	51.0	29	52.0
▪ Mycophenolic acid derivative	70	55.0	40	56.0	30	54.0
o Mycophenolate mofetil	48	68.6	27	56.3	21	43.7
o Enteric coated mycophenolate mofetil	22	31.4	13	59.0	9	41.0
▪ Calcineurin inhibitors	115	91.0	64	90.0	51	91.0
o Cyclosporine	26	22.6	20	77.0	6	23.0
o Tacrolimus	89	77.4	44	49.4	45	50.6
▪ M-tor inhibitors	12	9.5	7	58.3	5	41.7
o Sirolimus	10	83.3	5	50.0	5	50.0
o Everolimus	2	16.7	2	100.0	0	0.0
▪ Azathioprine	22	17.0	13	18.0	9	16.0
▪ Leflunomide	1	0.8	0	0.0	1	2.0
Number of Doses of Medication per day						
▪ Once	3	2.4	1	1.4	2	3.6
▪ Twice	79	62.0	45	63.4	34	60.8
▪ Three times	23	18.1	15	21.0	8	14.3
▪ Four times	10	7.9	6	8.5	4	7.0
▪ Five times	5	3.9	2	2.8	3	5.4
▪ More than five times	7	5.5	2	2.8	5	8.9

Characteristic	Total Population		Men		Women	
	Count	%	Count	%	Count	%
Treated for Transplant Rejection						
▪ Yes	4	3.0	0	0.0	4	7.0
▪ No	121	95.3	70	98.6	51	91.0
▪ Unsure	2	1.6	1	1.4	1	1.8
Function of Transplanted Organ						
▪ Working very well	109	85.8	63	88.7	46	82.0
▪ Working ok/some organ failure	10	7.9	5	8.9	5	8.9
▪ Not working well/severe organ failure	8	6.3	3	4.2	5	8.9
Other Medical Conditions*						
▪ Heart Condition	12	9.4	9	12.7	3	5.4
▪ High Blood Pressure	61	48.0	36	50.7	25	44.6
▪ Lung Disease	5	3.9	1	1.4	4	7.0
▪ Diabetes	29	22.8	22	31.0	7	12.5
▪ Ulcer or Stomach Disease	5	3.9	3	4.2	2	3.6
▪ Bowel Disease	12	9.5	5	7.0	7	12.5
▪ Kidney Disease	18	14.2	8	11.3	10	17.9
▪ Liver Disease	3	2.4	2	2.8	1	1.8
▪ Anemia or Other Blood Disease	9	7.0	1	1.4	8	14.3
▪ Cancer	7	5.5	6	8.5	1	1.8
▪ Depression	5	3.9	2	2.8	3	5.4
▪ Osteoarthritis, Degenerative Arthritis	17	13.4	8	11.3	9	16.0
▪ Back Pain	18	14.2	10	14.1	8	14.3
▪ None	19	15.0	11	15.5	8	14.3
▪ Other Medical Problems	36	28.3	14	19.7	22	39.3
Kidney Disease/Failure						
▪ No	81	63.8	51	71.8	30	53.6
▪ Yes, Mild Kidney Disease	13	10.0	7	9.9	6	10.7
▪ Yes, Moderate Kidney Disease	9	7.0	5	7.0	4	7.0
▪ Yes, Severe Kidney Disease	2	1.6	0	0.0	2	3.6
▪ Yes, On Dialysis	4	3.0	2	2.8	2	3.6
▪ Unsure	1	0.8	0		1	1.8
▪ I Have Had a Kidney Transplant[1]	17	13.4	6	8.5	11	19.6

* Respondents were allowed multiple answers for these questions [1]All participants were asked whether they had some degree of kidney disease, which is commonly caused by immunosuppressive medications. Many patients that had a kidney transplant chose the option of 'I have had a kidney transplant', instead of quantifying their kidney disease.

5.4.3 Symptom Experience

Respondents reported a median of 19 different adverse symptoms (IQR= 12- 27). In addition to the symptoms included on the MTSOSD, eight individuals reported additional symptoms that were not covered by the questionnaire. Two respondents reported tinnitus with a moderate level of distress, while another participant reported the occurrence of dry eyes, and peeling of skin of hands (reported as mildly distressing). Loss of sense of smell, agitation, bone weakness, and white outs, were also reported (each by one individual), and were all considered highly distressing.

Adverse Symptoms Occurrence and Distress

Respondents were asked to indicate whether they had experienced the adverse effect within the last four weeks on a scale of 'never (0)' to 'always (4)'. Symptoms prevalence was reported as the proportion of people who reported the occurrence of the symptom (scores of 1 and higher). Symptoms were then classified into tertiles according to occurrence (high, medium, and low occurrence), while associated distress via each of symptom was presented as mean score. Tables 4 and 5 depict the tertiles of symptom occurrence, arranged in descending order of distress for female and male respondents, respectively.

In both women and men, the most frequently reported commonly perceived symptoms were tiredness, flatulence, and lack of energy (reported at an incidence of 84%, 82% and 70% for women and 80%, 76%, and 66% for men, respectively).

The most prevalent symptoms were not necessarily the most distressing ones. In women, flatulence occurred in over 80% of the population, but was not perceived to be very distressing (mean 1.5 on a scale of 0 to 4). Diarrhea, however, occurred in 50% of the population, but was moderately distressing (mean 2.5/4). The most distressing adverse symptom in women was genital warts (mean 3.5/4), yet this symptom was only reported in 7% of respondents. Some distress levels were gender specific. For instance, breast enlargement occurred in a higher prevalence in men compared to women (13% vs. 5%), and men found the symptom to be more distressing (2 compared to 1/4, respectively). In men there seemed to be more consistency between occurrence and distress, as the most prevalent symptoms were usually the more distressing ones. With the exception of genital warts and puffy face in females (3.5/4 and 2.7/4, respectively), distress scores for adverse symptoms were generally moderate in nature (2.5/4 or less).

Table 4. Symptom distress versus prevalence among women after solid organ transplant

Symptom Distress	Symptom Prevalence		
	Low Prevalence (5-23%)	**Medium Prevalence (23.1-44%)**	**High Prevalence (44.1-84%)**
0.0-1.0	abnormal skin color red face/neck swollen glands swollen gums		
1.1-2.0	spots on face/neck oily skin constipation change in sense of taste altered voice fat on neck/back change in appearance warts o hands/feet hearing loss breast enlargement	warm hands/feet palpitations itching urgent urination chest pain ↑ appetite heartburn sores on lips/mouth ↓ appetite numb hands/feet swollen ankles/feet ↑ hair growth sensitivity to light	bruises ↑ thirst ↑ sweating flatulence brittle fingernails muscle cramps dryness of skin mood swings restlessness back pain dizziness headaches anxiety seeing difficulties trembling hands
2.1-3.0	menstrual problems skin rash puffy face	↓ interest in sex nightmares hair loss dyspnea brittle skin muscle weakness stomach complaints	depression tiredness sleeplessness ↓ memory lack of energy diarrhea joint pain
3.1-4.0	genital warts		

Symptom prevalence represents the proportion of patients that have experienced the adverse symptom (i.e. respondents who chose 'occasionally', 'regularly', 'almost always' or 'always' for symptom occurrence). Symptoms within each prevalence category were arranged from lowest to highest distress (scale=0 to 4).

Table 5. Symptom distress versus prevalence among men after solid organ transplant

Symptom Distress	Symptom Prevalence		
	Low prevalence (1-19%)	**Medium prevalence (19.1-39%)**	**High prevalence (39.1-80%)**
0.0-1.0	genital warts swollen glands		
1.1-2.0	change in appearance fat deposit n neck/back palpitations redness face/neck warm hands/feet change in sense of taste altered voice breast enlargement chest pain swollen gums ↓ appetite constipation puffy face abnormal skin color warts on hands/feet ↑ hair growth sensitivity to light	nightmares ↑ sweating sores on lips/mouth stomach complaints skin rash ↑ appetite dyspnea hair loss heartburn mood swings brittle fingernails headaches seeing difficulties anxiety spots on face/neck oily skin numb hands/feet urgent urination brittle skin itching ↓ interest in sex	dizziness depression muscle cramps swollen ankles/feet ↑ thirst back pain restlessness diarrhea hearing loss ↓ memory muscle weakness dryness of skin bruises trembling hands joint pain
2.1-3.0			erectile problems sleeplessness lack of energy flatulence tiredness
3.1-4.0			

Symptom prevalence represents the proportion of patients that have experienced the adverse symptom (i.e. respondents who chose 'occasionally', 'regularly', 'almost always' or 'always' for symptom occurrence.). Symptoms within each prevalence category were arranged from lowest to highest distress.

In a sensitivity analysis, we re-examined prevalence of adverse symptoms after applying a stricter definition of occurrence (i.e., only symptoms rated as the most prevalent symptoms identified by patients as a 3 or 4 (almost always or and always were counted)) (Table 6). In women, the three most prevalent adverse symptoms were dryness of skin, tiredness and reduced interest in sex (25%, 24% and 21% reported as almost always or always, respectively), while in men the three most prevalent symptoms were erectile problems, sleeplessness, and brittle skin (18%, 16% and 13%, reported as almost always or always, respectively). Tiredness (in women) was the only symptom that remained in the top three, when using the more stringent definition of occurrence. Also, the overall prevalence of adverse symptoms now reached only 25%, compared to the original definition, which resulted in an adverse event rate up to 84%.

Table 6. Top 10 adverse symptoms reported by women and men, according to the definition of 'almost always and always' on the occurrence scale

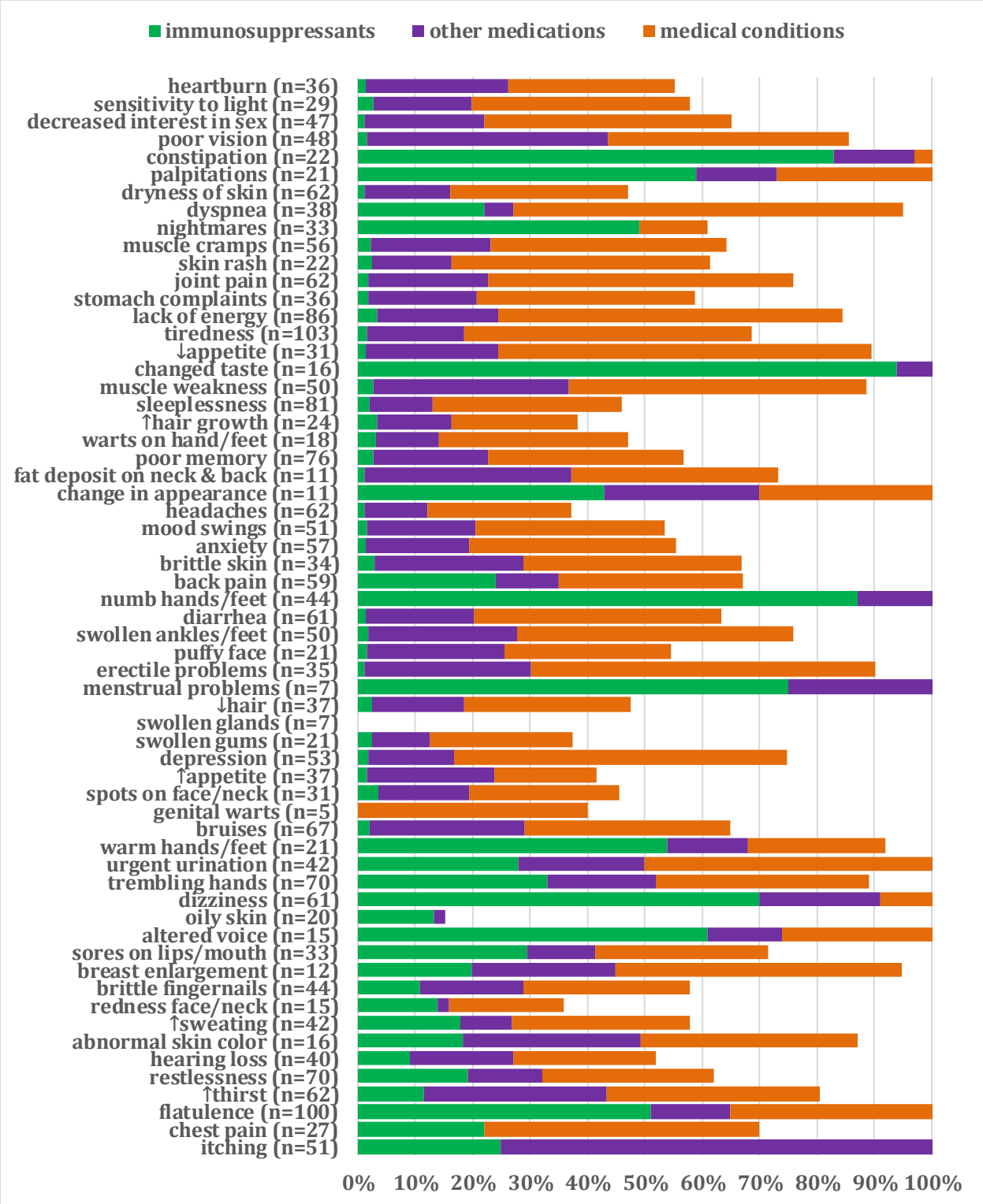
Women		**Men**	
Adverse Symptoms	**Proportion of patients (%)**	**Adverse Symptoms**	**Proportion of patients (%)**
dryness of skin	25.0	erectile problems	18.3
tiredness	23.6	sleeplessness	15.5
↓interest in sex	21.4	brittle skin	12.7
lack of energy	19.6	lack of energy	11.3
sleeplessness	18.0	bruises	11.3
brittle fingernails	18.0	↓interest in sex	11.3
muscle weakness	18.0	flatulence	10.0
trembling hands	16.0	joint pain	10.0
bruises	16.0	trembling hands	10.0
flatulence	14.3	dryness of skin	10.0

Causal Attribution of Adverse Symptoms:

Respondents were asked whether they attribute their adverse symptoms to immunosuppressant medications, other medications, and their medical conditions on a Likert scale of 'strongly agree' to 'strongly disagree'. For respondents that agreed or strongly agreed with immunosuppressants as a symptom cause, the specific immunosuppressant medications identified in the demographic section of the survey were presented in a follow up question to probe further into patient perceptions of each agent's role in causing the adverse symptom.

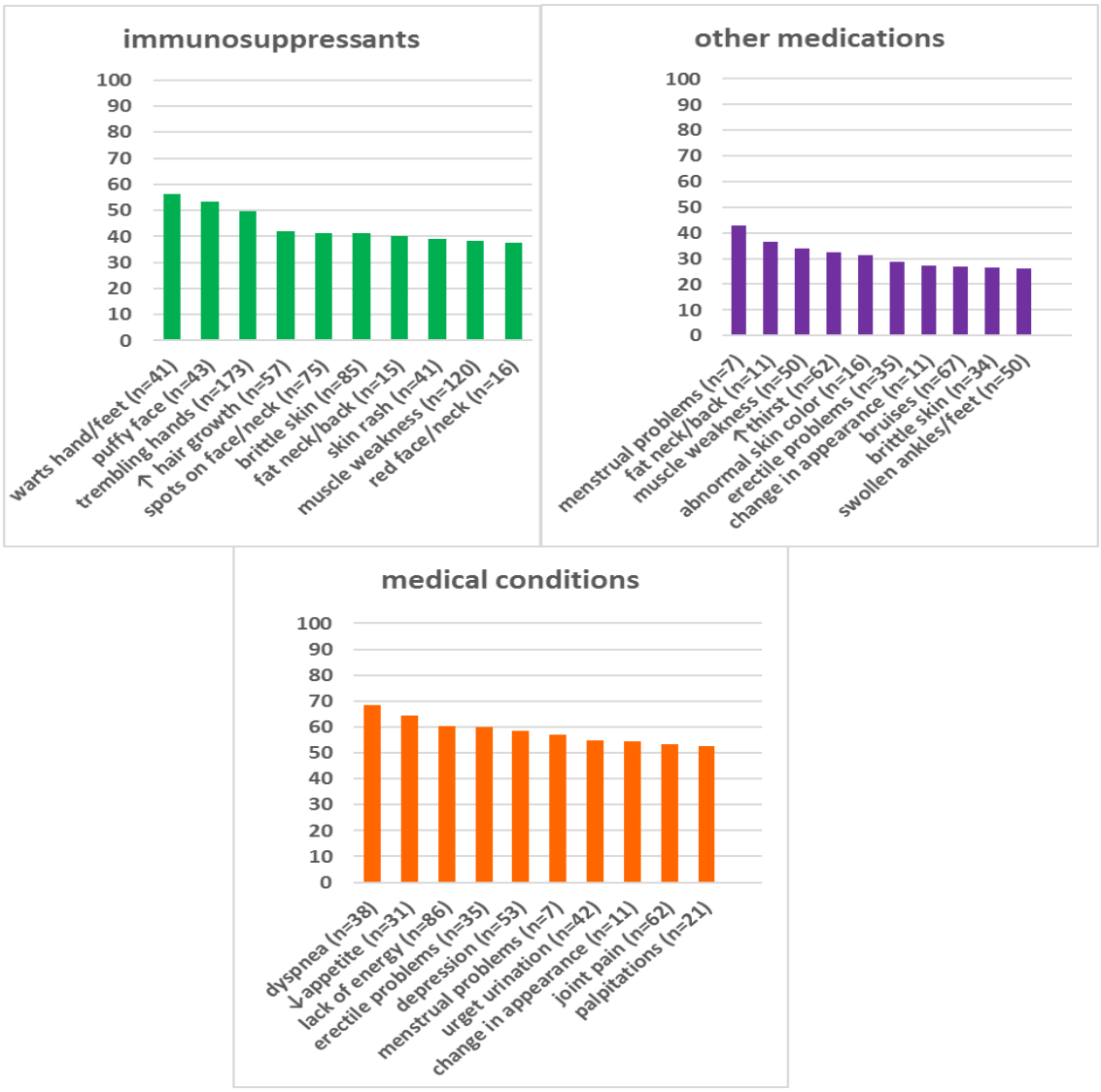
Overall, medical conditions were perceived to be the leading cause of adverse symptoms, followed by immunosuppressant medications, and other medications, respectively (Figure 2). Shortness of breath, poor appetite and lack of energy were perceived to be the top three symptoms caused mainly by medical conditions, while menstrual problems, fat deposits on neck and back, and muscle weakness were perceived to be caused by other medications. The top three symptoms perceived to be caused by immunosuppressant medications were warts on hands and feet, puffy face, and trembling hands (Figure 3).

Figure 2. Causal attribution of adverse symptoms



This figure presents the percentage of respondents that agreed or strongly agreed with the 3 potential causes for each adverse symptom.

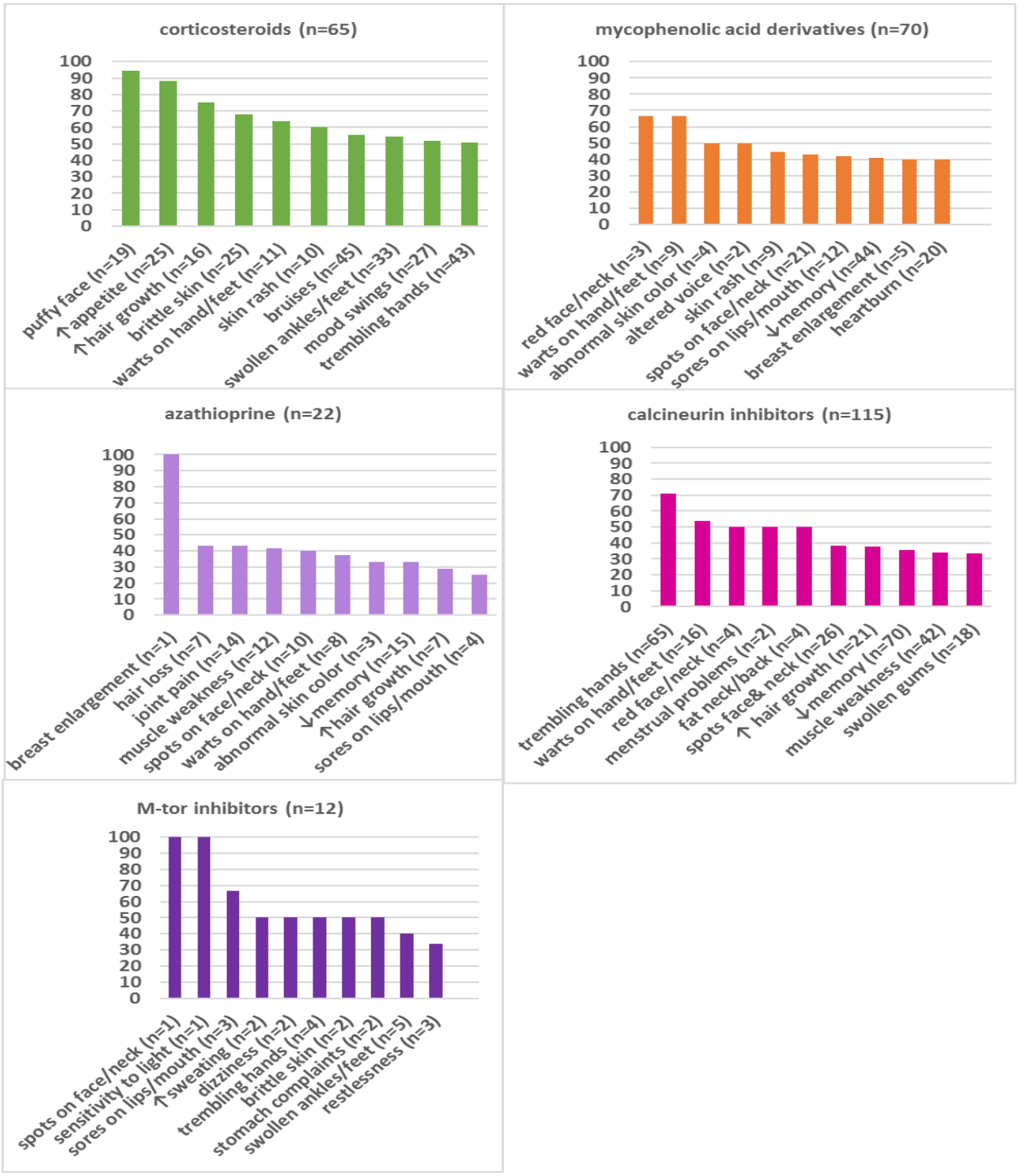
Figure 3. Top 10 symptoms attributed to immunosuppressants, other medications and medical conditions



This figure presents the top 10 symptoms attributed to immunosuppressants, other medications and medical conditions, according to the percentage of respondents that 'agreed' or 'strongly agreed'. The X-axis presents the ASI, where n= the number of respondents who reported the symptom. The Y-axis presents the percentage of respondents that 'agreed' or 'strongly agreed'.

Of the respondents that were taking calcineurin inhibitors (cyclosporine or tacrolimus), trembling hands, warts on hands and feet, and fat deposit on neck and back were the most common symptoms attributed to these medications. The leading adverse symptoms perceived to be caused by corticosteroids (prednisone) were puffy face, increased appetite and hair growth. The top 10 symptoms attributed to be caused by each immunosuppressive class are listed in figure 4. It should be noted that these results should be taken into context of the number of patients experiencing the symptoms. For instance, the top 4 ASI perceived to be caused by mycophenolic acid derivatives (mycophenolate mofetil and enteric coated mycophenolate sodium) were redness on face and neck, warts on hands and feet, abnormal skin colour and altered voice (reported by 65%, 65%, 50% and 50%, respectively). These symptoms, however, were only reported by a small number of participants (n=3, n=9, n=4, and n=2, respectively).

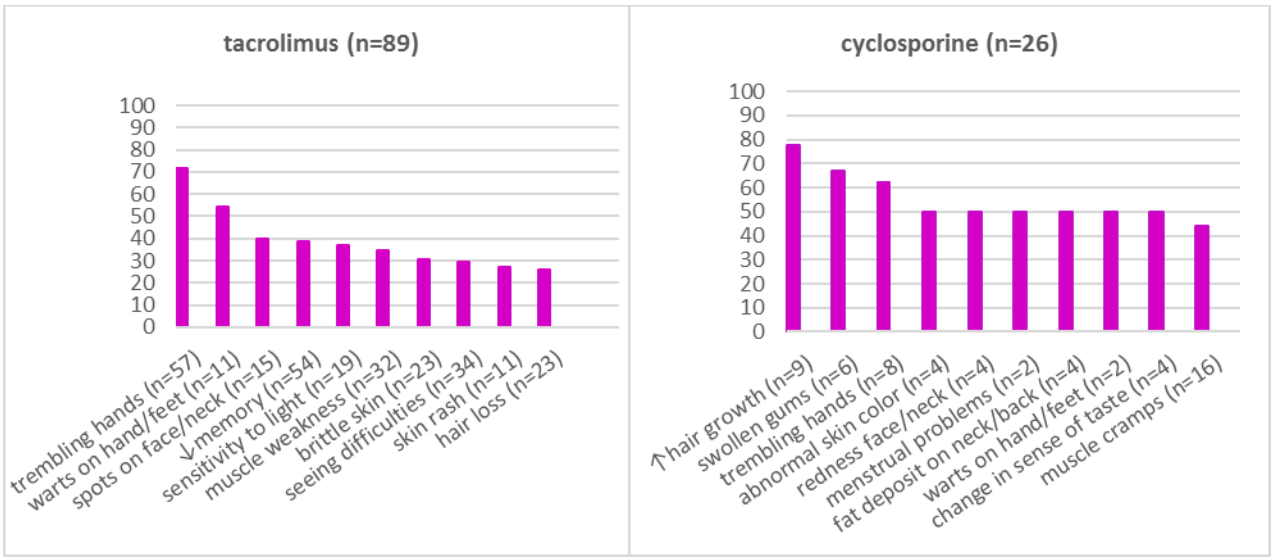
Figure 4. Immunosuppressant medications groups' attribution of adverse symptoms to immunosuppressant medications



This figure presents the top 10 symptoms attributed to specific immunosuppressant medications. The X-axis presents the ASI, where n= the number of respondents who reported the symptom. The Y-axis presents the percentage of respondents that 'agreed' or 'strongly agreed'.

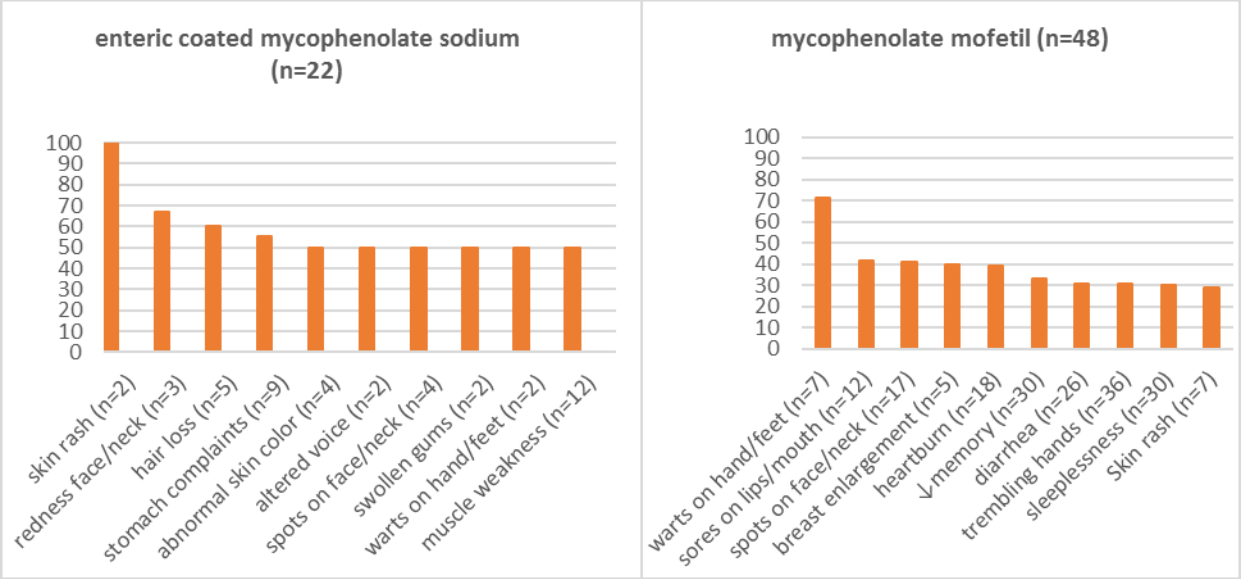
Adverse symptoms were not consistently reported among patients taking immunosuppressants from the same medication classes. For instance, respondents taking cyclosporine reported increased hair growth (78%), swollen gums (67%) and trembling hands (63%) as the top three attributed adverse symptoms, whereas respondents taking tacrolimus reported trembling hands (72%), warts on hands and feet (55%), and spots on face/neck (40%). Figures 5, 6 and 7 highlight these differences by comparing ASI attributed to specific agents within class. As with figure 4, the number of patients experiencing the symptoms should be taken into account when considering these results.

Figure 5. Calcineurin inhibitors attribution to adverse symptoms



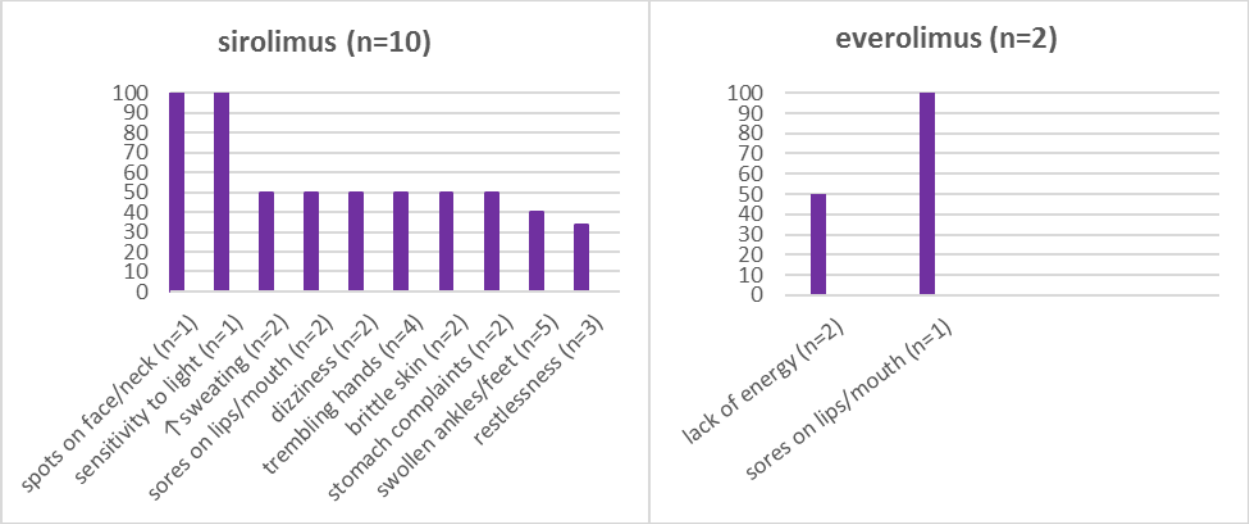
This figure presents the top 10 symptoms attributed to tacrolimus and cyclosporine, according to the percentage of respondents that 'agreed' or 'strongly agreed'. The X-axis presents the ASI, where n= the number of respondents who reported the symptom. The Y-axis presents the percentage of respondents that 'agreed' or 'strongly agreed'.

Figure 6. Mycophenolic acid derivatives attribution to adverse symptoms



This figure presents the top 10 symptoms attributed to enteric-coated mycophenolate sodium and mycophenolate mofetil, according to the percentage of respondents that 'agreed' or 'strongly agreed'. The X-axis presents the ASI, where n= the number of respondents who reported the symptom. The Y-axis presents the percentage of respondents that 'agreed' or 'strongly agreed'.

Figure 7. M-tor inhibitors attribution to adverse symptoms



This figure presents the top 10 symptoms attributed to sirolimus and everolimus, according to the percentage of respondents that 'agreed' or 'strongly agreed'. The X-axis presents the ASI, where n= the number of respondents who reported the symptom. The Y-axis presents the percentage of respondents that 'agreed' or 'strongly agreed'.

Adverse Symptoms Treatability:

Respondents reported the perceived treatability of each adverse symptom on a Likert scale of 'strongly agree' to 'strongly disagree'. The percentage of participants who agreed, or strongly agreed was calculated for each of the adverse symptoms. Lack of energy, warts on hands and feet, and headaches were ranked the highest in terms of treatability, as reported by 30% (13/39 women, 13/47 men), 72% (6/9 women, 7/9 men), and 72 % (22/34 women, 22/27 men), respectively. On the other hand, breast enlargement, changed taste, and nightmares received the least proportion of 'strongly agree' and 'agree' responses by 0% (0/3 women, 0/9 men), 6% (1/10 women, 0/6 men) and 6% (1/19 women, 1/14 men), respectively (Figure 7).

Figure 8. Treatability of adverse symptoms

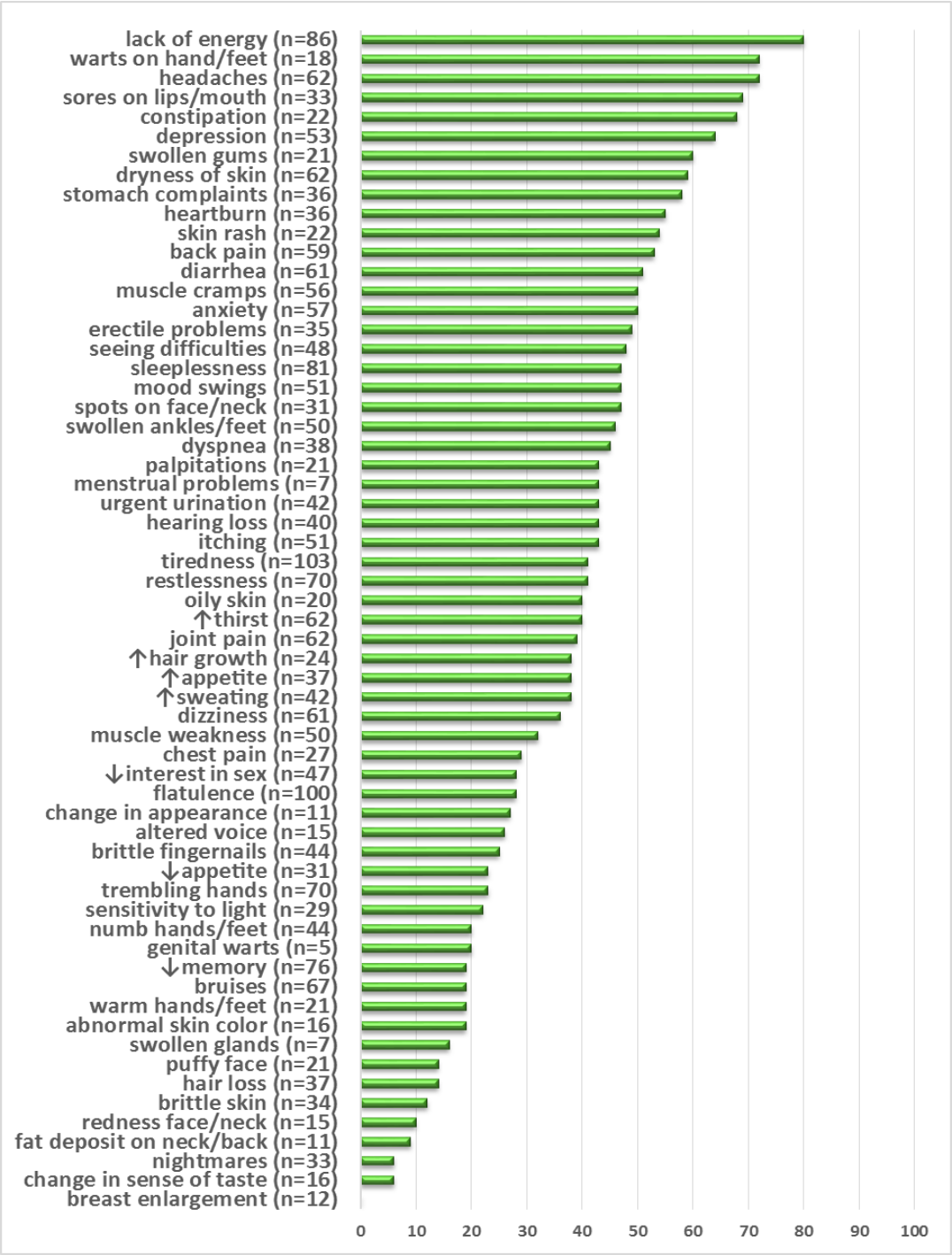


Figure 7 represents the proportion of respondents who 'strongly agreed' or 'agreed' when asked whether each symptom was perceived to be treatable. n= the total number of respondents who experienced each adverse symptom.

5.4.4 Quality of Life:

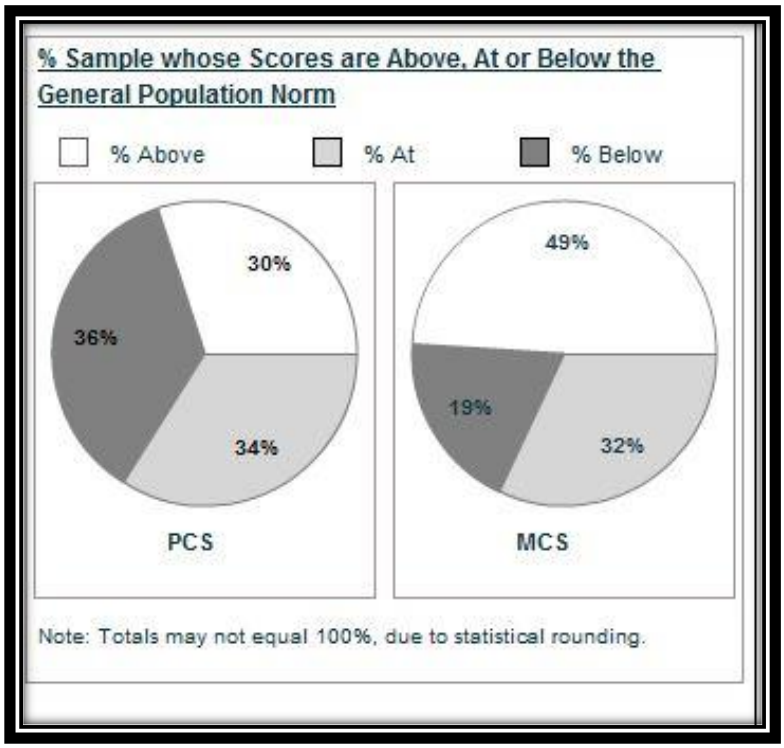
One hundred and thirteen transplant recipients (89% of respondents) completed the health-related QoL section, including 63 men and 50 women. The adjusted norm-based values (with a score of 50 equating to the US average ± standard deviation of 10) are presented in table 7, while Figure 8 indicates the percentage of patients that were above, at or below the population norm for the physical and mental component summaries (PCS and MCS). Both women and men reported a comparable physical component summary (47 and 48, respectively) and mental component summary (51 and 53, respectively) relative to a population norm. Women and men also reported a good overall general health (51 and 53, respectively) and good mental health (51 and 54, respectively).

Table 7. Quality of life scores for solid organ transplant recipients

Short Form-12 (SF-12) items	Women scores	Men scores
Physical component summary (PCS)	**46.5**	**48.1**
physical functioning (PF)	46.5	48.2
role physical (RP)	44.9	46.9
bodily pain (BP)	48.5	50.3
general health (GH)	51.3	52.5
Mental component summary (MCS)	**51.0**	**52.9**
vitality (VT)	48.7	50.6
social functioning	48.9	51.3
role emotional (RE)	48.9	49.5
Mental health (MH)	51.0	53.9

Respondents provided feedback on physical and mental health status, ability to do usual activities and how they rate their general health. Answers were summed up and compared to a control healthy population using SF-12 software.

Figure 9. Comparison of QoL scores to general population norms



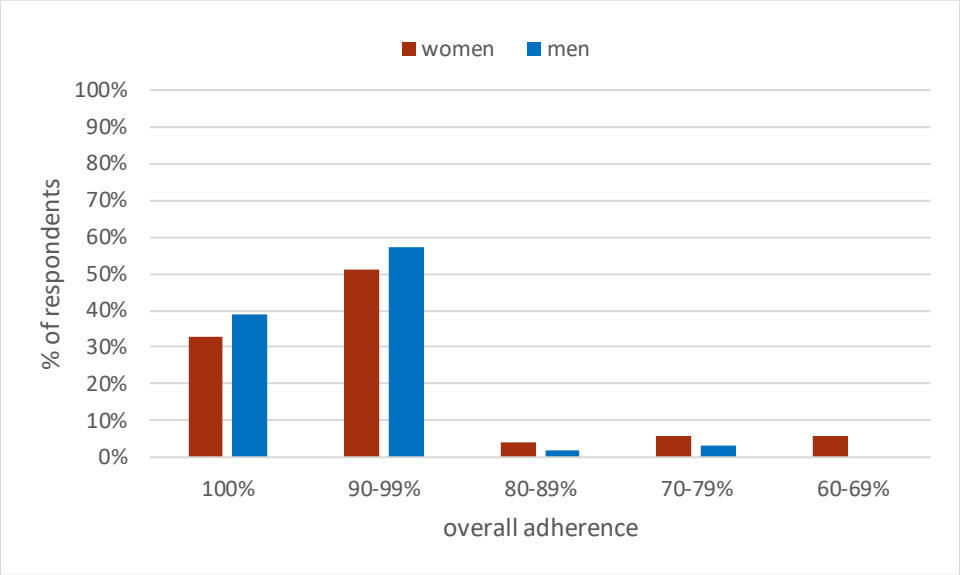
5.4.5 Self-Reported Adherence:

Over half (56%) of the respondents answered 'yes' to at least one of the four BAASIS questions, and were therefore categorized as nonadherent. Most cases were related to implementation of medication taking: 38% had missed a dose in the last four weeks, 4% have skipped two or more doses, 37% had taken their medications two hours before or two hours later than scheduled. One female transplant recipient (1% of total population) reported discontinuing at least one medication. Females and males were found to have similar rates of nonadherence (57%, and 55%, respectively) (Table 8). However, according to the visual analogue scale, more than two thirds of respondents (78%) reported that they had taken their immunosuppressive medications at the scheduled times most of the time (90-100%) (Figure 9).

Table 8. Self-reported adherence to immunosuppressant medications

1a. Implementation: Do you remember missing a dose of any of your anti-rejection medications in the last 4 weeks?			
	Women (n=49)	**Men (n=62)**	**Total (n=111)**
Yes	41.0% (20)	36.0% (22)	37.8% (42)
(If yes): Can you remember how often this happened?			
Once	55.0% (11)	59.0% (13)	57.0% (24)
Twice	20.0% (4)	18.0% (4)	19.0% (8)
Three times	20.0% (4)	9.0% (2)	14.3% (6)
Four times	0.0% (0)	4.5% (1)	2.4% (1)
>Four times	5.0% (1)	9.0% (2)	7.0% (3)
1b. Do you remember having skipped two or more doses of your anti-rejection medications in a row in the last 4 weeks?			
Yes	4.0% (2)	3.0% (2)	3.6% (4)
(If yes): Can you remember how often this happened?			
Once	50.0% (1)	50.0% (1)	50.0% (2)
Twice	50.0% (1)	0.0% (0)	25.0% (1)
Four times	0.0% (0)	50.0% (1)	25.0% (1)
2. Your anti-rejection medications need to be taken at specific times, recommended by your transplant team. Do you remember having taken your anti-rejection medications more than 2 hours before or after the recommended dosing time in the last 4 weeks?			
Yes	36.7% (18)	37.0% (23)	36.9% (41)
(If yes): Can you remember how often this happened?			
Once	10.0% (5)	14.5% (9)	34.0% (14)
Twice	14.3% (7)	11.3% (7)	34.0% (14)
4-5 times	8.8% (4)	9.7% (6)	24.4% (10)
Every 2-3 days	4.0% (2)	1.6% (1)	7.3% (3)
Almost daily	0.0% (0)	0.0% (0)	0.0% (0)
3. Have you altered the prescribed amount of your anti-rejection medications during the last 4 weeks, without your doctor telling you to do so?			
Yes	4.0% (2)	1.6% (1)	2.7% (3)
4. Discontinuation: Have you stopped taking your anti-rejection medications completely within the last year, without your doctor telling you to do so?			
Yes	2.0% (1)	0.0% (0)	0.9% (1)

Figure 10. Self-reported adherence using the visual analog scale (VAS) score



This graph represents the percentage of women and men who reported different scores on the visual analog scale when asked: '*how well did you do in the last 4 weeks with taking their anti-rejection medications using a visual analog scale, where 100% is 'always took medication as prescribed' and 0 is 'never'?'*

5.5 Objective 5: Assess Feasibility

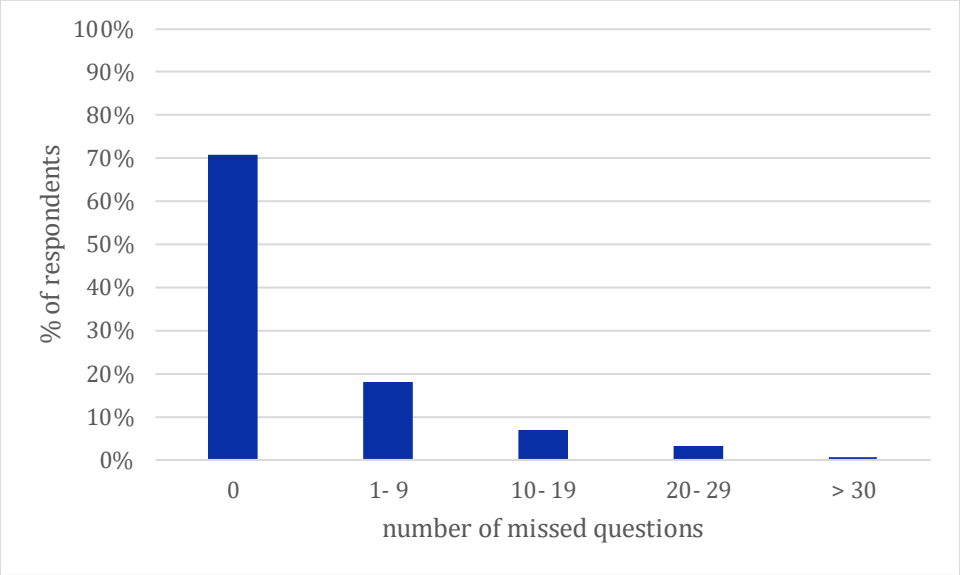
5.5.1 Response rate:

The survey was sent electronically to 249 members of the Canadian Transplant Association. A total of 127 questionnaires were returned achieving a response rate of 51% (127/249), exceeding our target response rate of 40%.

5.5.2 Missing of data:

Almost 71% of the survey respondents completed the entire questionnaire. The breakdown and description of missing data is reported in table 9. The questions that were most commonly missed were the causal attribution of adverse symptoms, as well as the as quality of life and adherence to immunosuppressive medications questions.

Figure 11. Summary of missed questions for returned surveys



5.5.3 Patient feedback

Forty transplant recipients (32%) provided open-ended comments. After a thorough review of the qualitative data, the following themes emerged: 1) Demographics and Clinical Conditions, 2) Survey Design, 3) Technical Issues.

Theme 1: Demographics & Clinical Conditions

Twelve respondents commented that many of their answers were influenced by the presence of other diseases or medical conditions. They believed their other medical conditions, or the medications used to prevent/treat them impacted their responses. For instance, patient#6 responded: *"[I am] presently limited with activity due to having surgery on my ankle and still recovering. Also on pain medications, therefore; a few questions like constipation and some mood effects that I wouldn't normally experience, have been answered with yes but are normally a no"*.

Transplant recipients (n=5) also acknowledged the influence of time since transplant with respect to symptom experience. Patient#6 stated,*" I have noticed that I would have experienced tons of adverse symptoms immediately after my transplant, some I would have experienced over the next five year period, then some I didn't experience until I hit about 15 years post-transplant"*. According to patient#49, *"In my case I had most of the complications and side effects in the first two years after transplant, time and treatment solved most of the issues and after five years now I consider myself in a great shape for my age"*.

Some respondents (n=5) indicated that many of their adverse symptoms could be age-related. As stated by patient#7: *"My responses for many of the questions reflects my age, seventy five years old"*, and patient#105: *"My age may be the reason for a number of my medical problems, or may not"*.

Theme 2: Survey Design

Three respondents suggested having more open ended questions, adding more space for elaborated answers and comments, and adding an 'Unsure' option to the answers. One of the respondents suggested replacing the 61 adverse symptoms with a blank space where patients can report their own experienced side effects. Patient #35: "*I think your data quality would be greatly improved if you asked the questions: Do you experience (symptom x)? If yes, do you think this is a side effect of your medications? If yes, then expand the list".* Patient#21 responded, *"[It was] hard to answer some of the questions. For example, some are not yes/no questions and perhaps after the first section there should be a comment section".*

While three respondents described the survey as lengthy, they felt this was necessary to cover the many adverse symptoms experienced by transplant recipients. Patient#61: *"I thought it was a little long, but it did ask very relevant questions".* Patient#101 responded, *"This is a daunting survey. It is very long, mainly because of the many-many side effects that these medications can cause. I would suggest breaking up the pages even more so that they can be saved and come back to it more often".*

Theme 3: Technical Issues

During the data collection phase of the study, we received feedback from a couple of respondents that the survey could not be completed on an iPad, which was an inconvenience. One respondent also filled out the survey using his cell phone, and acknowledged having some issues. These technical difficulties may have been caused by the complex skip logic/branching of the symptom experience questions.

A couple of respondents commented that there was a technical error regarding the skip logic (i.e. immunosuppressive medications that were not chosen by the respondent were still displayed when they should not have been). As noted by patient#91 *"Imuran popped up on one of the questions even though I don't take it and didn't identify that I took it".*

A few other technical comments were reported as well:

Patient#117 *"This survey wasn't mobile friendly and numerous times I would chose my answer and have to wait a few minutes before the question would expand to explain my answer".*

Patient#127 *"If a question is missed, please bring up that question only or highlight it rather than having us have to scroll through the full page".*

Patient#17 *"When a person misses a question, it should give a question number to go back to not just the topic. There were several hundred questions in the 60 categories".*

CHAPTER 6: DISCUSSION

The results of this pilot indicate that it is feasible to assess symptom experience, quality of life, and adherence to immunosuppressants in a cohort of solid organ transplant recipients using a single electronic survey. The pilot involved representatives of varying ages, transplant type and provincial location, and achieved a satisfactory response rate of 51%. Data analysis was completed within a reasonable amount of time, and 71% completed the entire questionnaire without missing a question.

This pilot study also identified issues that require more attention prior to undertaking a multicenter study. Further review and testing is recommended to improve the questionnaire design, and technical issues identified by the respondents. A subgroup analysis should also be incorporated into the statistical plan, to evaluate any association between age, other medical conditions and time post-transplant on symptom experience, QoL, and nonadherence to immunosuppressive medications.

Transplant recipients face several new challenges after transplantation. Transplant recipients may experience ASI, which can impact their physical and psychological well-being and health-related quality of life. ASI may also contribute to nonadherence to prescribed immunosuppressants, consequently leading to rejection and graft loss. It is essential for health care professionals to assist patients with adapting to post-transplant changes and to develop strategies to manage ASI, to maximize transplant recipient's general health. Our descriptive study was designed to explore transplant recipient's perceptions on their symptom experience, quality of life and nonadherence to immunosuppressive medications. This chapter presents a discussion of the study results in four principal sections: 1) tool identification, questionnaire development and piloting, 2) descriptive analysis, 3) feasibility of future multicenter study, 4) strengths, and limitations.

6.1 Tool Identification, Survey Development and Piloting

Since this was the first study to evaluate symptom experience, quality of life, and nonadherence to immunosuppressive medications in a group of solid organ transplant recipients there was no pre-existing tool to measure the three areas collectively. Therefore, a literature review was undertaken to identify quantitative tools that were previously used in transplant literature to measure these target areas. Our final questionnaire was comprised of the MTSOSD,

SF-12, and BAASIS to measure symptom experience, quality of life, and nonadherence to immunosuppressive medications, respectively.

The three tools used in our questionnaire were validated in previous literature (MTSOSD: transplant recipients, SF-12: dialysis population, BAASIS: chronic conditions (HIV-positive),[45,48,49,87,118,119] therefore the research team decided not to revalidate the final tool; instead it was revised and edited by the advisory committee and a transplant physician. Furthermore, the questionnaire was tested by10 lay people and finalized.

6.2 Descriptive Analysis

6.2.1 Respondents Demographics and Clinical Situation

Participants in our survey had similar demographics to those reported in US and European registries of solid organ transplant populations in terms of age, sex, and ethnicity (Table 10).[120,121] Our study population was notably different, however, in that there was a higher proportion of liver (33%) and heart (23%) transplant recipients and a lower proportion of kidney (23%) transplant recipients.

Since immunosuppressive medication regimens may differ by organ, caution is needed when generalizing these findings to other transplant populations with a different organ composition. Time since transplant should also be taken into consideration when extending our findings to other populations. The average time since transplant in our study was more than 6 years. Since immunosuppression and symptom experience can change over time, these results may not reflect the experiences of patients who were more recently transplanted.

Table 9. Demographic and clinical variables according to Canadian, American and European registries versus our study population

	Canadian Institute of Health	**United Network for Organ Sharing (US)**	**Euro- transplant Organisation**	**Our Study**
Gender (% male)	NA	62%	NA	55%
Age (in years)	NA	Mean = 57	Median = 55	Mean = 55
Ethnicity	NA	European decent 56%	NA	European decent 71%
Transplant type (by % organ)	Kidney 59% Heart 6% Liver 22%	Kidney 58% Heart 9% Liver 23%	Kidney 56% Heart 9% Liver 24%	Kidney 23% Heart 23% Liver 33%

6.2.2 Symptom Experience

To define the most commonly occurring symptoms, prevalence was calculated as the percentage of respondents that reported the occurrence of the symptom. Our approach was consistent with a previous study of kidney transplant patients from European transplant centers (n= 1209) that reported symptom occurrence in prevalence (percentage of respondents who reported any occurrence of the adverse symptom, meaning 1 or more).[52] Likewise, a study of HIV positive patients used this approach to identify the most commonly occurring adverse symptoms.[122] To describe symptom distress we used the mean score for each symptom, which is similar to how distress was defined in the previously mentioned HIV positive study.[122]

In our study, the most prevalent symptoms in women and men were tiredness, flatulence, and lack of energy. This finding is consistent with previous studies that have used the MTSOSD.[14,30,52] A study of kidney transplant recipients (n=356) in Switzerland found that tiredness was the most common symptom,[14] while another study (n= 261) reported tiredness (88.8%) and lack of energy (79.5%) as the most prevalent symptoms in heart transplant recipients.[30] Likewise, a study investigating symptom experience in 543 kidney transplant recipients reported the most prevalent symptoms to be flatulence (73.9%), tiredness (73.0%) and lack of energy (63.9%).[52]

The most prevalent symptoms were not necessarily the most distressing in our study. Although they occurred infrequently (7%), women in our study reported genital warts as the most distressing symptom, same for skin rash (prevalence 11%, distress 2.2 on a scale of 0 to 4) and menstrual problems (prevalence 13%, distress 2.1 on a scale of 0 to 4). Amongst men, tiredness, flatulence, and erectile problems were both frequent and distressing (prevalence/distress 80% /2.2, 76% /2.2 and 49% /2.1, respectively). These results are similar to another study of 261 heart transplant recipients, in which tiredness, lack of energy and nervousness were reported to be the most common symptoms by men and women, while the most distressing symptoms were erectile dysfunction in men, decreased interest in sex (men and women) and muscle weakness in men.[30] This is also similar to the findings of a study in 356 kidney transplant recipients, where women reported painful menstruation, rash and mouth infections and men reported anxiety, mouth infections and swollen gums as least frequent/highly distressing.[14] It is interesting to note that, in general, our participants seemed to report a good

overall QoL comparable to general public despite high prevalence of adverse symptoms and the associated perceived distress. A similar study (quantifying distress using the same approach) in a more acute population would be interesting, since our transplant recipients on average were transplanted at least six years ago.

Even general comparisons of symptom prevalence and distress between previous research and our results are somewhat difficult, since previous studies used different definitions and analysis to characterize symptom experience (occurrence and perceived distress). Our findings seem to be in line with transplant literature in that female respondents reported more symptoms and a higher perceived distress than men.[16,47-49]

Causal attribution and treatability of adverse symptoms from the perspective of transplant recipients were of particular interest in this study. Since the literature is sparse regarding these aspects of patient perception and we could not find any studies addressing patient perception of symptom causal attribution and treatability in solid organ transplant recipients, we looked into the literature of other chronic diseases. In a study of HIV-positive adult patients exploring the symptom causal attribution, participants mainly attributed their adverse symptoms to HIV infection, followed by antiretroviral medications.[122] Our transplant recipients primarily attributed their adverse symptoms to their medical conditions, followed by immunosuppressive medications and other medications. Our survey tool asked patients to identify which specific immunosuppressant was perceived to be the causative factor. In many cases, respondent's perceptions of the cause of specific side effects were consistent with the literature. For example, corticosteroids were frequently identified as a cause of puffy face, increased appetite and hair growth; cyclosporine was identified as a cause of increased hair growth, tacrolimus caused trembling hands, and sirolimus caused stomach disturbances. In contrast, some drugs were blamed for side effects that were not reported in the literature; azathioprine was cited as the cause of breast enlargement and joint pain but no such association could be found in the product monograph. Similarly, oral sores, spots on face and neck, and skin rash were attributed to mycophenolic acid derivatives where no such link could be found in the product monograph or other literature. It is not clear whether patients attribute adverse events to specific drugs because of a personal evaluation of their symptoms or if they are basing these associations on their knowledge of drug side effects reported in drug information materials. Understanding how patient experiences, expectations and knowledge may influence their symptom experience would

be very valuable. Future research is needed to determine whether the perceived cause of adverse symptoms is associated with lower medication adherence.

Treatability of adverse symptoms from a patient perception is another understudied area in the literature of chronic conditions. Our sample perceived lack of energy and warts on hands and feet to be the most treatable symptoms, while breast enlargement and changes in sense of taste received the least agreement on their treatability. This information is of value and utility for health care providers as understanding the patient's perception on cause and treatability of ASI may ultimately assist with understanding underlying factors that may contribute to nonadherence. For instance, if an immunosuppressive medication is largely perceived to responsible for causing an ASI that is particularly bothersome and this ASI is not perceived to be treatable, patients may be more likely to stop this medication. To our knowledge, this study is the first to investigate cause and treatability from a patient perspective, and we believe more research should be undertaken in this area.

6.2.3 Quality of Life

Since patient perceptions of ASI may influence their reported QoL, it was important for us to investigate this concept in this research. Interestingly, participants in this study reported comparable health-related quality of life to that of general public. Most of the previous studies in this area have noted transplant recipients to have a similar or slightly lower QoL to that of the general public. In a study of heart transplant recipients, however, participants reported a higher physical (57.0) and mental quality of life (58.0) than normal population,[84] which may be due to the fact that patients in this study were 20 years or more post-of transplant and those who received a re-transplantation or a multi-organ transplants were excluded. In our population, the mental component summary scores (MCS) were reported as 51.4 and the physical component summary scores (PCS) were 47.4. This trend was consistent with another study of 722 solid organ transplant recipients that used SF-12 to evaluate QoL, which revealed a MCS score of 50.2 and PCS score of 42.6.[55]

The World Health organization definition of quality of life focuses primarily on the subjective perception of individuals that may be guided by physical, psychological state and personal beliefs. Thus, the positive QoL scores reported in this study may be due to our sample of generally healthy, stable transplant recipients. In general, the members of the CTA are a highly functional and active group of recipients that advocate for organ donation and are

involved in national and international transplant Olympic games. A study conducted in the 1990s assessing QoL in transplant recipients who were competing in United States Transplant Games found similar results, as participants reported a comparable overall QoL to that of the general population.[123] Another explanation for the positive QoL scores reported in this study maybe due to transplant recipient's perception of improvement from their pre-transplant situation. Transplant is a lifesaving procedure for many, which reduces the physical and economic burden for medical procedures such as dialysis. Hence, QoL scores would be expected to improve after transplant. A study of kidney transplant recipients used the Crisis theory as a conceptual framework to justify this idea.[124] More specifically, the Crisis theory suggests that the QoL of people in crisis deteriorates, therefore they are more willing to try new coping methods and learn to adapt to their situation which leads to a QoL which is comparable or even better to that of less severely ill patients or healthy individuals in subsequent stages of the disease.[125] The aforementioned study of kidney transplant recipients included three different groups: Candidates waiting for transplant (n=45), transplant recipients (n=99) and non-transplant population (n=82). [124] The finding was in agreement to our finding, as transplant recipients reported a better QoL compared to candidates on the wait list with end stage organ failure, and a comparable QoL to non-transplant recipients. It is reassuring that the transplant recipients in our study reported a comparable QoL to general population even though they were taking an average of seven medications and reported a median of 19 different adverse symptoms.

6.2.4 Adherence to Immunosuppressive Medications

The overall self-reported nonadherence rate was 56% in our population. This seems to be consistent with the results of a study of kidney transplant recipients (n=62), in which respondents reported an overall nonadherence of 65% using BAASIS dichotomous scale.[110] On the other hand, participants in our study reported a lower nonadherence rates using the visual analog scale, as 78% of participants reported 90-100% adherence to immunosuppressive medications. The possible explanation for the differences in overall adherence using dichotomous (answers of the four questions) versus continuous approach (the visual scale) could be due to the strict definition of nonadherence, according to the dichotomous approach; any yes answer to one of the four questions classifies the respondent as non-adherent. The discrepancies between the dichotomous approach and the visual analogue scale have been noted in two other studies. In the previously mentioned study of 62 kidney transplant recipients, 65% of respondents reported nonadherence

to immunosuppressive medications using the dichotomous scale, while the median overall adherence reported using the visual analog scale was 99.5%.[110] In another study of 238 solid organ transplant recipients, of 35.3% reported nonadherence on the dichotomous scale, while they reported a high overall adherence (median scores of 95%) using the continuous visual analog scale. [104] It should be noted that the results of the BAASIS dichotomous cannot be directly compared to those of the continuous scale since there is no threshold score for non-adherence on the continuous visual analogue scale. This is because it is impossible to define the level of non-adherence that would result in negative clinical consequences – i.e. there is no "acceptable" level of non-adherence.

Adherence to immunosuppressive medications is fundamental to graft survival and improving outcomes. However, measuring nonadherence is a controversial topic as there are different methods following different definitions for nonadherence. Solid organ transplant relevant methods can be classified into direct or indirect. Direct methods involve measuring levels of drug or metabolites in the blood or urine, which requires a clinical setting. A downside to those methods is their high cost in terms of labour and laboratory work. Inaccurate results may be obtained as a result of medication timing – i.e. if the patient ingested their medication immediately before blood sampling.[126] Indirect methods include patient self-report, reports from physicians or family members, refill rates, pill counts, or electronic monitoring.[126] Most of the indirect methods are economic and easy to use but may be less sensitive, except for electronic monitoring which is a technologically advanced method that registers the opening of medication bottles. Opening the bottle, however, cannot definitively confirm that the patient actually took the medication. Interestingly, one study has shown that that transplant recipients seem to over report nonadherence using self-reported methods compared to electronic monitoring and assay values.[104] Many authors have recommended combining direct methods of measuring along with self reported tools to measure adherence in order to improve accuracy, Still, there is no agreed on gold standard to measure nonadherence to immunosuppressive medications and discrepancies may occur as a result of the method of measure, so it is difficult to compare our study results to other studies. Nevertheless, the purpose of this study was to capture the perspectives of patients, and the data obtained from the self-reporting adherence scale provides valuable information about our cohort's perceptions of adherence.

6.3 Feasibility of Future Multi-Center Study

This pilot study provided important insights on transplant recipient's perceptions of symptom experience, quality of life and nonadherence to immunosuppressive medications. A future multicenter study, however, should be undertaken to assess these aspects in a more diverse population. Our study response rate of 51% and the completion rate of 71% were acceptable, considering the length of the questionnaire. Based on response rate and completion rate alone, our results suggest that it could be feasible to use this questionnaire for future studies. Nevertheless, several other considerations would be required to complete this survey in a healthcare setting. Administering a paper copy of this questionnaire is not an option due to the questionnaire's length, and the complex skip logic required for many of the questions. Consequently, a laptop or a tablet would be needed for participants to fill out the survey, and a research assistant, or dedicated staff member would be necessary to distribute devices to those who need them. Completing this survey requires undivided attention and time, which may be difficult for patients in a busy dynamic clinic setting. Hence the arrangement of an assigned space would need to be considered to administer this questionnaire in a clinic or hospital setting. The associated expenses to these details needs to be accounted for when planning a future study. Another idea to consider with the cost and time investment would be to conduct the survey in an interview setting, minimizing complexity and resolving any clarity issues.

Our experience with the pilot study helped us to understand ways in which the survey could be improved. For instance, for the symptom causal attribution questions we asked the respondent to rate whether 'immunosuppressive medications', 'other medications' and 'medical conditions' caused each ASI, using a separate Likert scale for each potential cause. In the future, we could consider combining the three questions, or asking the participant whether they believe each symptom is a side effect of the immunosuppressive drug(s), as suggested by patient #35. This will help eliminate unnecessary length of the questionnaire and reduce the time needed for questions to load. Some patients in our study also indicated that they had difficulties attributing their adverse symptoms to a specific immunosuppressive medication, and suggested we include the option of 'I don't know'. This feedback will be taken into consideration for the next stage of the project.

6.4 Strengths and Limitations

Identifying transplant recipient's perception of their post-transplant life is important for designing any future interventions. Our study adds to existing literature by highlighting prevalence, perceived distress in a sample of solid organ transplant recipients, and exploring new aspects to symptom experience by gathering feedback on causality and treatability of symptoms. Moreover, it also evaluated QoL and nonadherence to immunosuppressive medications.

A distinction of this study is that it is the first study to evaluate symptom experience, QoL and nonadherence to immunosuppressive medications in a national cohort of solid organ transplant recipients, achieving an excellent response rate and a high attrition rate for the survey completion. Variables were measured using instruments with established validity in chronic illnesses populations, which enhances the quality of the results.

Several limitations of this study need to be considered. Convenience sampling was used to recruit participants for this study and targeted adult solid organ transplant recipient members of the Canadian Transplant Association. Patient demographics and our observed results suggest that this cohort likely represents a healthier, more stable population than the average transplant recipient. Furthermore, the results may be subject to volunteer bias, suggesting that within our sample, patients who are more stable were more likely to complete the survey compared to those who are in a worse health condition.[127] As previously discussed, caution is warranted when generalizing the results of this study to other populations.

A self-reported questionnaire was used in this study, which has its own challenges. Although the survey was anonymous, it is possible that participants may have responded to the questionnaire in manner they perceived to be more positive or acceptable, way, rather than providing an honest description of their experiences. The adherence section may be particularly vulnerable to this type of bias. Since many of the questions in this instrument are subjective rather than factual, patients may interpret the Likert scales used in the study differently. For instance, with respect to perception of ASI, what one person might consider severe, another may consider mild or moderate, leading to discrepancies in reporting. Finally, we asked the participants to report their individual perceptions and experiences from the last four weeks, which may have given rise to inaccuracies due to recall bias.

Our survey data was collected on one occasion, and we acknowledge that symptom experience, QoL and adherence may vary over time. Patient feedback confirmed this; some

respondents commented that administering the survey at a time closer to transplantation would yield different responses since certain ASI may be are more prevalent at that time. Other respondents acknowledged that they had various symptom experiences at different times post-transplant. In our study, most of the respondents (61%) were transplanted at least six years ago, using this 'snap-shot' approach as we have, may have led to an under- or over-estimates of ASI occurrence. Future studies should examine the effect of time since transplant on over ASI occurrence in and aim for a more heterogeneous population.

There was no control group in this study to identify differences in symptom experience between transplant recipients and non-transplant recipients. Consequently, we were unable to ascertain whether the reported symptoms are also experienced by the general population, and if in fact they are a consequence of transplantation. We included questions to ascertain the perceived cause of the adverse effects, however, since this area has been largely unexplored in previous research.

Although the questionnaire consisted of three validated tools, its final formatting was not tested for validity and internal reliability. This may have resulted in problematic or unidentified issues such as ambiguity of some questions; however, consultation with experts and testing on 10 lay people were done to minimize these problems. The questionnaire contained only one open-text comment box at the end of the survey. For example, patient#21 wrote: "*Hard to answer some of the questions, for example, some are not yes/no questions, and perhaps after the first section there should be a comments section*." In the future, the addition of open-text comments boxes for each section would enable the respondents to elaborate in their feedback and enhance capturing respondent's perceptions.

Technical issues such as the survey not being iPad or mobile friendly, and other issues such as the malfunction of skip logic for some questions may have led to incomplete questionnaires. Some difficulties also occurred with survey distribution. Because the survey was sent through the CTA, there was no way to track undeliverable emails or incorrect email addresses. It was not possible to know which transplant recipients had received the survey emails and who had not. This information would have been useful in determining the true response rate and minimizing any potential non-response bias. Moreover, the CTA executive requested us to decrease the number of emails sent to their members, which may have affected our response rate.

Nevertheless, our response rate of 51% is comparable or better than to that of other electronic surveys.

In this study the interrelationship between symptom experience, QoL and nonadherence to immunosuppressive medications were not explored. The objectives of this study were to identify relevant tools, develop a tool, pilot test it and perform descriptive analysis to characterize symptom experience, QoL and nonadherence in a sample of solid organ transplant recipients. Furthermore, as this was a pilot study to assess feasibility of a future study, studying the interrelationship is recommended as a target of future research.

6.5 Conclusions

To our knowledge this study was the first to explore patients' perception on causal attribution and treatability of adverse symptoms, as well as assessing symptom experience, quality of life, and nonadherence to immunosuppressive medications collectively in a sample of solid organ transplant recipients. The intersection of perceived distress versus frequency revealed that higher prevalent symptoms are not necessarily the most distressing ones. In general, transplant recipients reported a good QoL and adherence to immunosuppressive medications, despite experiencing a high number of adverse symptoms. Future study should expand on the information generated from this pilot, extending this research into other settings with a more diverse transplant population, and investigating the interrelation of symptom experience, QoL and nonadherence.

Appendix A: Advance Letter/Survey Invitation

Dear Member of the Canadian Transplant Association,

Our names are Holly, Shirin and Jennifer and we are pharmacists who work and do research in transplantation. We are contacting you today to see if you might be interested in helping us with our latest study.

As health care professionals working with transplant patients, we know that transplant medications may cause side effects that are bothersome or that may affect your daily activities. The purpose of this survey is to find out what side affects you as a transplant patient find most bothersome, how they affect your life, and your ability to take medications.

We hope that the knowledge gained from this research will help us understand the things that we can do to help people take their anti-rejection medications, improve transplant care and have healthier transplant patients. Your opinions and experiences as a transplant patient are very important in carrying out this project.

We know that your time is valuable and limited, but we hope you will feel that this project is as important as we do. By taking part in this survey you can make a difference in the care of transplant patients! Completing the survey should take 30 to 45 minutes. Your answers in the survey will be anonymous and your decision to take part is voluntary. There is no risk to participation and your refusal to take part will not affect your transplant care in any way.

As a token of our appreciation for your participation, we are offering a $10 Tim Horton's gift card. If you would like to receive the gift card, we will need to collect your name and address, so that we can mail it to you. After you have completed the survey you will be directed to an optional link to provide us with your mailing information. Your survey responses will not be linked to your personal information (so we will have no way of identifying your responses). To complete the survey, please go to the link below:

Patient Survey on Side Effects of Transplant Medications

If the link above does not work, try copying the link below into your web browser:

https://redcap.usask.ca/redcap/surveys/?s=D8FNMTFNR7

This survey is hosted by REDCap, a USA owned company and subject to US laws. As such the privacy of the information you provide may be subject to the laws of that jurisdiction. By participating in this survey you acknowledge and agree that although your answers will be

stored in Canada they may or may not receive the same level of privacy protection afforded by Canadian law. Your responses in the survey, however, will remain anonymous.

By completing the survey, **YOUR FREE AND INFORMED CONSENT IS IMPLIED** and indicates that you understand the above conditions of participation in this study.
The deadline for completing the survey is May 10, 2015.

This research project has been approved on ethical grounds by the University of Saskatchewan Research Ethics Board. Any questions regarding your rights as a participant may be addressed to that committee through the Research Ethics Office ethics.office@usask.ca (306) 966-2975. Out of town participants may call toll free (888) 966-2975. If you have any questions about the project itself, you may contact Holly Mansell at (306) 966-1512 or holly.mansell@usask.ca. Results of the survey will be shared with the CTA membership either by email or by posting the results on the CTA website.

We are grateful for your help and thank-you for being an important part of this project!

Sincerely,
Shirin Aladwin, BScPharm, MBA
Pharmacist/Graduate Student
University of Saskatchewan

Holly Mansell, PharmD
Transplant Pharmacist/Advisor
University of Saskatchewan/Saskatchewan Transplant Program

Jennifer Harrison, BScPharm, MSc
Transplant Pharmacist/Project Co-lead
Toronto General Hospital, University Health Network

Appendix B: First Reminder

Dear Member of the Canadian Transplant Association,

A week ago, you received an email inviting you to take part in a survey about transplant medications. The purpose of the survey is to learn more about your experiences with side effects of transplant medications so that we can manage them better.

- If you have already completed the survey, we thank you very much for your help with this project! We apologize for sending you another email – since the survey is anonymous, our research team has no way of identifying which members have already completed the survey.
- If you have not had a chance to complete the survey yet, we would still love to hear from you! To make this project a complete success we still need 120 additional respondents to complete the survey. If you have partially completed the survey, you still have the opportunity to complete it - unfortunately we can only use fully completed surveys. The survey will be open until May 10.

To complete the survey, please go to the link below:

Patient Survey on Side Effects of Transplant Medications

If the link above does not work, try copying the link below into your web browser:

https://redcap.usask.ca/redcap/surveys/?s=D8FNMTFNR7

As a token of our appreciation for your participation, we are offering a $10 Tim Horton's gift card. If you would like to receive the gift card, we will need to collect your name and address, so that we can mail it to you. After you have completed the survey you will be directed to an optional link to provide us with your mailing information. Your survey responses will not be linked to your personal information (so we will have no way of identifying your responses).

This survey is hosted by REDCap, a USA owned company and subject to US laws. As such the privacy of the information you provide may be subject to the laws of that jurisdiction. By participating in this survey you acknowledge and agree that although your answers will be stored in Canada they may or may not receive the same level of privacy protection afforded by Canadian law. Your responses in the survey, however, will remain anonymous.

By completing the survey, **YOUR FREE AND INFORMED CONSENT IS IMPLIED** and indicates that you understand the above conditions of participation in this study.

The deadline for completing the survey is May 10, 2015.

This research project has been approved on ethical grounds by the University of Saskatchewan Research Ethics Board. Any questions regarding your rights as a participant may be addressed to that committee through the Research Ethics Office ethics.office@usask.ca (306) 966-2975. Out of town participants may call toll free (888) 966-2975. If you have any questions about the project itself, you may contact Holly Mansell at (306) 966-1512 or holly.mansell@usask.ca. Results of the survey will be shared with the CTA membership either by email or by posting the results on the CTA website.

We are grateful for your help and thank-you for being an important part of this project!

Sincerely,

Shirin Aladwan, BScPharm, MBA
Pharmacist/Graduate Student
University of Saskatchewan

Holly Mansell, PharmD
Transplant Pharmacist/Advisor
University of Saskatchewan/Saskatchewan Transplant Program

Jennifer Harrison, BScPharm, MSc
Transplant Pharmacist/Project Co-lead
Toronto General Hospital, University Health Network

Appendix C: Final Reminder

Dear Member of the Canadian Transplant Association,

On behalf of the research team we want to send our sincere thanks for your help with our survey on side effects of transplant medications! We apologize for any technical inconvenience that you may have experienced, and that the survey cannot be completed on an ipad. We have noticed that a number of participants have started, but not yet completed the survey. Many of you are so close! We hope that you will consider answering a few more questions, as your input is truly important to us. This is the final email you will receive - the close date has been extended to May 24, 2015.

Thanks again,
Shirin, Holly and Jennifer.

To complete the survey, please go to the link below:
Patient Survey on Side Effects of Transplant Medications
If the link above does not work, try copying the link below into your web browser:
https://redcap.usask.ca/redcap/surveys/?s=D8FNMTFNR7

As a token of our appreciation for your participation, we are offering a $10 Tim Horton's gift card. If you would like to receive the gift card, we will need to collect your name and address, so that we can mail it to you. After you have completed the survey you will be directed to an optional link to provide us with your mailing information. Your survey responses will not be linked to your personal information (so we will have no way of identifying your responses).

This survey is hosted by REDCap, a USA owned company and subject to US laws. As such the privacy of the information you provide may be subject to the laws of that jurisdiction. By participating in this survey you acknowledge and agree that although your answers will be stored in Canada they may or may not receive the same level of privacy protection afforded by Canadian law. Your responses in the survey, however, will remain anonymous.

By completing the survey, **YOUR FREE AND INFORMED CONSENT IS IMPLIED** and indicates that you understand the above conditions of participation in this study.

This research project has been approved on ethical grounds by the University of Saskatchewan Research Ethics Board. Any questions regarding your rights as a participant may be addressed to that committee through the Research Ethics Office ethics.office@usask.ca (306) 966-2975. Out of town participants may call toll free (888) 966-2975. If you have any questions about the project itself, you may contact Holly Mansell at (306) 966-1512 or holly.mansell@usask.ca. Results of the survey will be shared with the CTA membership either by email or by posting the results on the CTA website.

Thanks again for your help with this important project!

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